ORIGINAL

Before the
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

In re: Food Labeling; Health Claims and Label Statements; Request for Scientific Data and Information	)	**Docket No. 91N-0098**
	)	**(Fiber and Colorectal Cancer)**

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SUPPLEMENTAL COMMENTS OF JULIAN M. WHITAKER, M.D.; MYCOLOGY RESEARCH LABS, LTD; PURE ENCAPSULATIONS, INC.; WEIDER NUTRITION INTERNATIONAL, INC.; XCEL MEDICAL PHARMACY LTD; THE AMERICAN PREVENTIVE MEDICAL ASSOCIATION; AND DURK *PEARSON* AND SANDY SHAW.

Julian M. Whitaker, M.D.; Mycology Research Labs, Ltd.; Pure Encapsulations, Inc.; Weider Nutrition International, Inc.; XCEL Medical Pharmacy, Ltd.; the American Preventive Medical Association; and Durk Pearson and Sandy Shaw (collectively, "Joint Commenters"), by counsel and in response to the notice seeking scientific data and information ("Notice") published in the Federal Register, 64 Fed. Reg. 48841-48842 (September 8, 1999) and 65 Fed. Reg. 4252-4253 (January 26, 2000), hereby submit these comments.

I. BACKGROUND OF COMMENTERS

Julian M. Whitaker, M.D. Julian M. Whitaker, M.D. is a physician licensed to practice medicine in the states of California and Washington. He graduated from Dartmouth College in 1966 with a B.S. degree and from Emory University in 1970 with an M.D. degree. He received additional training in surgery as a resident at the University

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of California Medical School. From 1975 to 1976 he worked as a physician at the Pritikin Institute in California. Since that time he has been the Clinical Director of the Whitaker Wellness Institute in Newport Beach, California. He is the author of five books: ***Reversing Heart Disease*** (1985), ***Reversing Diabetes*** (1987), ***Reversing Health Risk*** (1989), ***Natural Healing*** (1994), and ***What Your Doctor Won't Tell You About Bypass*** (1995). Since August of 1991 he has been the editor of ***Health & Healing***, currently the nation's largest single editor health newsletter. In 1998, ***Health & Healing*** had over 500,000 subscribers. He receives royalties from the distribution and sale of several dietary supplements based on formulas he develops and licenses. Among the supplements which Dr. Whitaker has formulated (and from which he receives or will receive royalty payments) is a lignin fiber based product. He wants to place the proposed health claim on the labels and in the labeling of his fiber dietary supplement and, but for FDA's extant bar on labeling use of the claim, he would do so. Accordingly, he seeks FDA approval of the claim.

Durk Pearson and Sandy Shaw. Pearson and Shaw are scientists residing in Nevada. They design dietary supplement formulations and license them to manufacturing and retailing companies. They are authors of four books on aging and age-related diseases, including the #1, million plus copy best seller ***Life Extension: A Practical Scientific Approach*** (1982). They have also published three other health books, two of which were best sellers: ***The Life Extension Companion*** (1984); ***The Life Extension Weight Loss Program*** (1986); and ***Freedom of Informed Choice—FDA Versus Nutrient Supplements*** (1993). Durk Pearson and Sandy Shaw were plaintiffs in the *Pearson v. Shalala* case. The agency identifies this proceeding as one to aid it in

implementing *Pearson's* mandate. Pearson and Shaw license dietary supplements that contain fiber. Pearson and Shaw wish to communicate the nutrient/disease relationship that is the subject of these comments on their fiber dietary supplement labels and in their labeling.

American Preventive Medical Association. The American Preventive Medical Association (APMA) is a non-profit organization located in Virginia. APMA was founded in October of 1992 and is dedicated to ensuring consumer access to preventive therapies and the rights of health care providers to offer those therapies. APMA was a plaintiff in the *Pearson v. Shalala* case. The agency identifies this proceeding as one to aid it in implementing *Pearson's* mandate. Several APMA physicians sell dietary supplements that contain fiber. APMA and its practitioner members and their hundreds of thousands of patients would benefit from approval of the health claim that is the subject of this proceeding because it would enable them to communicate and receive nonmisleading health information on labels and in labeling concerning the effects of fiber on reducing the risk of colorectal cancer. APMA and its member physicians, therefore seek agency approval of the claim.

Mycology Research Labs LTD. Mycology Research Labs LTD (Mycology) is a corporation organized in Great Britain engaged in the business of manufacturing, distributing, and selling multiple pharmaceutical grade dietary supplements for human consumption in the United States. Five of the dietary supplements manufactured and sold by Mycology contain fiber. Mycology wants to place the proposed health claim on the labels and in the labeling of those fiber supplements and, accordingly, Mycology seeks approval of the health claim.

Pure Encapsulations, Inc. Pure Encapsulations, Inc. (Pure) is a Massachusetts corporation engaged in the business of manufacturing, distributing, and selling over 250 pharmaceutical grade dietary supplements for human and companion animal consumption. One of the dietary supplements manufactured and sold by Pure for human consumption contains fiber. Pure would like to place the proposed health claim that is the subject of this proceeding on the label and in the labeling of that fiber dietary supplement.

Weider Nutrition International, Inc. Weider Nutrition International, Inc. (Weider) is a Utah corporation engaged in the business of manufacturing, distributing, and selling over 2,000 pharmaceutical grade dietary supplements for human and companion animal consumption. Weider has been a health, fitness and sports nutrition leader for nearly fifty years since its founding in 1939. Weider plans to manufacture and sell at least four dietary supplements that contain fiber. Weider would like to place the proposed health claim that is the subject of this proceeding on the labels and in the labeling of those fiber products.

XCEL Medical Pharmacy, Ltd. d/b/a XCEL Health Care. XCEL Medical Pharmacy, Ltd. d/b/a XCEL Health Care (XCEL) is a California corporation engaged in the business of manufacturing, distributing, and selling pharmaceutical grade dietary supplements for human consumption. One of the dietary supplements XCEL intends to manufacture and sell XCEL contains wheat and vegetable fiber. XCEL would like to use the proposed health claim that is the subject of this proceeding on the labels and in the labeling of those fiber products.

II. SUMMARY OF THE NOTICE

The Department of Health and Human Services (HHS), Food and Drug Administration (FDA), Center for Food Safety and Applied Nutrition (CFSAN) has published a Notice in the September 8, 1999 Federal Register, 64 Fed. Reg. 48841-48842, requesting scientific data, research study results, and other related information concerning four substance-disease relationships. On January 26, 2000, FDA announced in the Federal Register that it was reopening the comment period and would accept scientific data and written comments that are submitted on or before April 3, 2000. 65 Fed. Reg. 4252. In *Pearson v. Shalala,* 164 F. 3d 650 (D.C. Cir. 1999) *reh'g denied en banc*, 172 F.3d 72 (D.C. Cir. 1999), the U.S. Court of Appeals for the D.C. Circuit held four FDA sub-regulations (prohibiting each of the four substance-disease relationships) invalid under the First Amendment. (21 C.F.R. §§ 101.71(a), (c), (e); 101.79 (c)(2)(i)(G)). *Pearson*, 164 F. 3d 658. One of the four subregulations is the subject of this comment. That regulation, 21 C.F.R. § 101.71(a), prohibits the following claim: "consumption of fiber may reduce the risk of colorectal cancer."[1] The FDA Notice states that the agency will determine if an "appropriate scientific basis exists to support the issuance of a proposed rule to authorize a health claim for the relationship between fiber and colorectal cancer based on the data and information it receives." 64 Fed. Reg. 48841. FDA requests that interested parties submit scientific data and information published between 1992 and the present concerning the relationship.

[1] 21 C.F.R. § 101.71(c) in pertinent part reads: "Health claims not authorized for foods in conventional food form or for dietary supplements of vitamins, minerals, herbs, or other similar substances: Dietary Fiber and cancer."

III. THE PROPER LEGAL ISSUE BEFORE THIS AGENCY IS NOT WHETHER THE CLAIM WILL BE AUTHORIZED BUT, RATHER, WHAT KIND OF DISCLAIMER SHOULD BE USED

Under *Pearson*, this agency must authorize the fiber health claim. The Court rejected FDA's argument that the claim was inherently misleading. *Pearson*, 164 F. 3d at 656. The Court determined that the claim was, at worst, potentially misleading. 164 F.3d at 657. In accordance with Supreme Court commercial speech precedent, only inherently misleading claims may be suppressed outright. 164 F.3d at 659. Claims that are, at worst, potentially misleading must be authorized with corrective disclaimers. 164 F.3d at 656. Thus, because the First Amendment – and not the agency's own rules and policy preferences – is the Supreme law of the land, this agency must authorize the fiber health claim. The only legal question confronting the agency is precisely how to disclaim the claim to avoid a misleading connotation. In the first instance, the Court of Appeals has made that decision for the agency. 164 F.3d at 658-659.

IV. FDA MUST IMMEDIATELY AUTHORIZE THE CLAIM ON AN INTERIM BASIS WITH THE DISCLAIMER SPECIFIED BY THE *PEARSON* COURT

The *Pearson* Court held the agency's suppression of the fiber claim invalid under the First Amendment to the United States Constitution. *Pearson* 164 F. 3d at 659. It did so upon a complete record including all scientific evidence then before FDA. Having reviewed that evidence and the agency's arguments against claim authorization, it held the claim not inherently misleading but, at worst, only potentially misleading. *Pearson* 164 F. 3d at 656. Consistent with Supreme Court precedent, a potentially misleading claim must be authorized with disclaimers and may not be suppressed outright. *44 Liquormart v. Rhode Island,* 517 U.S. 484, 503 (1996). Relying on that precedent, the

Court of Appeals gave this agency a disclaimer it deemed sufficient to address the agency's concerns about misleadingness. When applied to the fiber claim, that disclaimer reads: "The evidence is inconclusive because existing studies have been performed with *foods* containing fiber, and the effect of those foods on reducing the risk of colorectal cancer may result from other components in those foods." 164 F. 3d at 656-659.

Because the rule FDA now enforces to prevent the claim from appearing on labels and in labeling is invalid, and because the Court has held the claim, at worst, only potentially misleading, FDA must no longer enforce the invalidated rule and must act immediately to allow the claim. Prudence dictates, and law necessitates, that this agency allow the claim on an interim basis with the disclaimer the Court crafted to cure misleadingness. That will ensure that the First Amendment rights of the Joint Commenters are not violated during the period of agency consideration of alternative disclaimers.

This agency has violated the *Pearson* Court's order by continuing to enforce the invalidated rule on the fiber claim from the time of the issuance of the Court's mandate (April 20, 1999) until the present, approximately one year as of the date of these comments. The agency's enforcement of the invalidated rule is an unlawful act that cannot stand. The federal courts have held that violations of constitutional rights, including First Amendment rights, must be rectified with haste and cannot be allowed to stand for years while the Government contemplates its next move. Indeed, the Supreme Court has held that violation of a First Amendment right, even for a very short period of time, constitutes irreparable injury without proof of more. See *Elrod v. Burns,* 427 U.S.

347, 373 (1976) (plurality opinion) ("The loss of First Amendment freedoms, for even minimal periods of time, unquestionably constitutes irreparable injury") quoted in *Jackson v. City of Columbus*, 194 F.3d 737, 747 (6th Cir. 1999); *Iowa Right to Life Comm., Inc. v. Williams,* 187 F.3d 963, 969 (8th Cir. 1999); *Brownsburg Area Patrons Affecting Change v. Baldwin,* 137 F.3d 503, 507 (7th Cir. 1998); *New York Magazine v. Metropolitan Transportation Authority,* 136 F.3d 123, 127 (2nd Cir. 1998); see also *City of Lakewood v. Plain Dealer Publishing Co.,* 486 U.S. 750, 758 (1988); *Washington Free Community v. Wilson,* 426 F.2d 1213, 1218 (D.C. Cir. 1969). When Government violates First Amendment rights, the Supreme Court has held delay in eliminating the rights violation intolerable: "Speakers . . . cannot be made to wait for years before being able to speak with a measure of security." *Riley v. National Federation of the Blind,* 784 U.S. 781, 793-94 (1988) (internal quotes omitted).

The Supremacy Clause of the Constitution establishes beyond per adventure of doubt that the Constitution and the laws in pursuance of it are supreme to contrary laws. U.S. Const. Art. VI, *Marbury v. Madison,* 5 U.S. 137, 178-180 (1803). Accordingly, this agency should not have continued to enforce the invalid rules beyond April 20, 1999, and clearly must immediately authorize the fiber claim on an interim basis with the disclaimer specified by the Court of Appeals. At the conclusion of its rulemaking on the fiber claim, FDA may then craft an alternative, permanent disclaimer, if deemed necessary, to cure any misleadingness the agency perceives based on the supplemental submissions it has solicited.

IV. RECENT SCIENTIFIC RESEARCH ADDS FURTHER EVIDENCE CONFIRMING COLORECTAL CANCER RISK REDUCTION EFFECTS OF FIBER

The evidence in support of the fiber claim is overwhelming. Recent studies confirm that conclusion. Since the Joint Commenters' initial submission in response to the agency's public notice, additional research has appeared in the peer-reviewed literature germane to the claim, all militating in favor of the claim.

Among the recent studies germane to the claim are the two described below and appended hereto as Exhibits 1 and 2. Based on the overwhelming body of publicly available scientific evidence, this agency should reverse its earlier decision and authorize the claim.

As explained below, even if the agency erroneously fails to approve the claim under its health claims review standard, it must nevertheless authorize it with a reasonable disclaimer because that authorization is required to avoid violation of the First Amendment to the United States Constitution.

In Exhibit 1 hereto (Reddy BS, "Prevention of colon carcinogenesis by components of dietary fiber," *Anticancer Res*, 1999, 19: 3681-3), the author presents a scientific review of the peer-reviewed literature concerning the chemoprotective effects of components of dietary fiber, especially wheat brant fiber. The studies provide evidence that dietary phytic acid found in fiber components is chemoprotective against colon cancer. The data show that specific components of fiber reduced the incidence of putative preneoplastic lesions in the colon. The authors conclude that: (1) case-controlled studies show reasonably strong evidence that dietary fiber reduces the risk of colon cancer in humans; (2) dietary intervention studies provide evidence that wheat bran supplementation decreases the levels of several putative tumor promoters in the colon;

and (3) administration of phytic acid, high levels of which are present in wheat bran and other grains, inhibits colon carcinogenesis in animal models.

In Exhibit 2 hereto (Williams GM, Williams CL and Weisburger, "Diet and Cancer Prevention: The Fiber First Diet," *Toxicol Sci,* 1999, 52 (2 Suppl): 72-86), the authors present a review of peer-reviewed scientific literature and document the role fiber plays in cancer prevention. Both soluble and insoluble fiber are "involved in inhibition of cancer risks by specific mechanisms." The evidence very strongly supports the conclusion that fiber is protective against colon cancer, especially fibers derived from cereals and vegetables. The evidence demonstrates that Americans need to increase fiber consumption to 25 to 35 grams per day and decrease overall caloric intake to reduce risk of colorectal cancers. At least 50% of those fiber grams should be from grains.

V. FDA MUST NOT ASSESS "SIGNIFICANT SCIENTIFIC AGREEMENT" BASED ON ITS PROPOSED "GUIDANCE" BECAUSE THE GUIDANCE VIOLATES *PEARSON*, THE INTENT OF CONGRESS, AND THE PLAIN LANGUAGE OF THE NLEA

On December 22, 1999, the FDA published a proposed "Guidance" in a failed attempt to comply with the *Pearson* Court's mandate that it define a standard for "significant scientific agreement." As explained in comments filed by the Joint Commenters in response to that guidance (attached hereto as Exhibit 3 and incorporated herein by reference), FDA may not require near conclusive proof as a condition precedent to approval of a dietary supplement health claim. Rather, Congress expects this agency to approve claims backed by "significant scientific agreement" without requiring them to satisfy the standard established by law for FDA approval of drugs (the "substantial evidence" standard in 21 U.S.C. § 355(e). The bi-partisan Senate Committee on Labor

and Human Resources explained in its Committee Report reviewing FDA's application of the health claims standard:

> **The committee notes that the significant scientific agreement standard is, by design, more flexible than the standard established by law for FDA to review and approve drugs, which requires a demonstration of safety and effectiveness based on "adequate and well-controlled clinical investigations." While the intake of a nutrient on which a health claim is based must be safe, there is no requirement that health claims be derived from clinical trials, and, by its terms, the standard recognizes that significant scientific agreement on the validity of the claim does not have to be complete. Evidence from a broad range of reliable scientific sources should be considered in determining the adequacy of scientific support.**

Senate Report 103-410, at 24.

In its Guidance, the FDA fails to fulfill the *Pearson* Court's ordered to explain what "significant scientific agreement" means and what it does not mean. The Guidance does not provide information necessary for regulatees to perceive FDA's guiding principles. While, from the Guidance, the regulated class can understand that FDA views interventional studies involving well designed randomized, controlled clinical trials as its "gold standard," it is entirely impossible from the Guidance to perceive whether FDA will ever accept studies other than interventional or other than those involving randomized, controlled clinical trials, as sufficient for claim authorization. Moreover, FDA requires proof of direct causality (that a substance ***will*** result in a change in a disease endpoint) as a condition precedent to claim approval. A large body of evidence strongly supporting, but not conclusively proving, a substance-disease relationship appears unlikely to satisfy FDA. Thus, the only principle that regulatees can perceive with clarity from FDA's Guidance is that FDA will accept the same kind of near conclusive proof expected as a condition precedent for drug approval as its basis for

dietary supplement claim approval. That principle, however, violates congressional intent as the excerpted passage above makes clear.

Congress plainly expects this agency to approve health claims for dietary supplements without requiring that those claims be backed by the same kind of near conclusive proof required for the grant of applications for new drugs. Accordingly, to the extent that FDA's Guidance reveals a principle to the regulated class, that principle is one calling for a level of evidence that Congress has unequivocally rejected in the context of health claims for dietary supplements. Consistent with the dictates of Congress, this agency should hold that significant scientific agreement exists when

> a significant segment of scientists having relevant expertise agree, based on relevant scientific evidence, that consumers are *reasonably likely* to obtain the claimed health benefit.

Senate Report 103-410, at 24. Congress has determined that the above-quoted definition which it supplied in committee is "consistent with the NLEA's goal of assuring that consumers have access on food and dietary supplement labels to health claims that are scientifically supported, without having to wait until the degree of scientific certainty contemplated by the drug standard has been achieved." *Id.*

Based on the hundreds of studies submitted to the FDA in this docket and the docket reviewed by the *Pearson* Court, there can be no doubt that "a significant segment of scientists having relevant expertise agree, based on relevant scientific evidence, that consumers are *reasonably likely* to obtain the claimed health benefit" for the claim that fiber may reduce the risk of colorectal cancer. Indeed, the evidence appears to surpass that expected by Congress for claim approval and to be approaching the near conclusive degree that FDA erroneously expects as a condition precedent for health claim approval.

Accordingly, FDA should, indeed it must, approve the claim under 21 U.S.C. § 343(r)(5)(D) and its rules as backed by "significant scientific agreement."

VI. ASSUMING *ARGUENDO* THAT FDA FAILS TO FIND "SIGNIFICANT SCIENTIFIC AGREEMENT," IT MUST NEVERTHELESS AUTHORIZE THE CLAIM WITH DISCLAIMERS CONSISTENT WITH *PEARSON*

Assuming *arguendo* that this agency decides that the fiber claim is not backed by "significant scientific agreement" and, thus, decides not to *approve* it, it may not deny the claim outright but must nevertheless *authorize* it with a corrective disclaimer. 164 F.3d at 656. Indeed, as explained above, FDA has a constitutional obligation to authorize the claim at the earliest possible moment. In light of the fact that the *Pearson* Court has already determined that the claim is not inherently misleading (164 F.3d at 656) and is, at worst, only potentially misleading, under applicable First Amendment precedent this agency has an incontrovertible duty to authorize the claim. That duty to authorize the claim trumps any contrary agency preference or rule and necessitates authorization with a disclaimer. U.S. Const. Art. VI, *Marbury,* 5 U.S. 178-180. That duty does not compel FDA to *approve* the claim, as the *Pearson* Court explained. *Pearson* at 164 F.3d at 659. Indeed, if FDA finds "significant scientific agreement" lacking, it may choose not to place its imprimatur of approval upon the claim; nevertheless, even without claim approval under significant scientific agreement, the First Amendment compels FDA to authorize unapproved claims so long as the claims can be rendered nonmisleading through the addition of a disclaimer. 164 F.3d at 659. In this case, the Court of Appeals has taken the extraordinary step of fashioning disclaimers for the agency's use. That action, coupled with the First Amendment burden upon government to rectify wrongful acts of suppression with haste, compels FDA to issue

immediately an interim rule authorizing the claim with the disclaimer specified by the Court. FDA may then arrest its unlawful enforcement of the constitutionally invalid rule and proceed with rulemaking to define precisely the content of the final disclaimer it desires to require for use with the claim.

VII. CONCLUSION

For the foregoing reasons, FDA must act immediately to authorize the fiber claim on an interim basis requiring use of the disclaimer crafted by the *Pearson* Court, as explained above. That action is warranted because the *Pearson* decision invalidated the rule FDA now enforces unlawfully to prevent use of the fiber claim. That action is also warranted because First Amendment precedent, cited above, requires immediate elimination of a civil rights violation, including a First Amendment right violation, by this government. Accordingly, FDA should immediately authorize the fiber claim with the corrective disclaimer specified by the *Pearson* Court. If, upon completion of its rulemaking, it fails to approve the claim under "significant scientific agreement," it must nevertheless authorize it with a disclaimer tailored to satisfy any other reasonable concerns the agency may have. In fact, based on the additional science adduced, FDA should approve the "may" claim without disclaimers in light of the fact that the claim is amply supported by "significant scientific agreement." To avoid a violation of the Administrative Procedure Act's prohibition on arbitrary and capricious agency action, FDA should interpret "significant scientific agreement" as Congress intended. Under the congressionally intended definition, the fiber claim should be *approved* by the agency. Nevertheless, if it is not *approved*, it should nevertheless be *authorized* with disclaimers, as required by the First Amendment.

Respectfully submitted,

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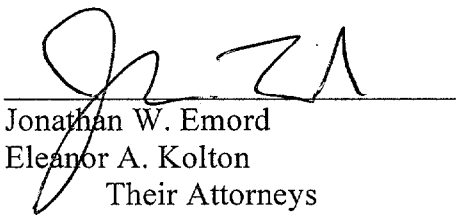

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EXHIBIT 1

ANTICANCER RESEARCH *19*: 3681-3684 (1999)

Prevention of Colon Carcinogenesis by Components of Dietary Fiber

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Abstract. *Cancer of the colon is one of the leading causes of cancer death in Western countries and is increasing rapidly in Japan. Epidemiological and laboratory animal madel studies have suggested an inverse relationship between colon cancer risk and intake of fiber-rich foods. The protective effect of dietary fiber which comprises a heterogeneous group of nonstarch polysaccharides such as cellulose, hemicellulose, and pectin and noncarbohydrate substances such as phytic acid depends on the nature and source of fiber in the diet. Laboratory animal madels have consistently shown that dietary administration of wheat bran reduced colon tumarigenesis. Human diet intervention studies have demanstrated that supplemental wheat bran in the diet decreased the formation of putative metabolites such as secondary bile acids and diacylglycerol in the colon that have been shown to act as tumor promoters in the colon. Among the components of dietary fiber, especially wheat bran, phytic acid (inositol hexaphosphate) has been studied extensively for its chemopreventive properties against colon carcinogenesis in the laboratory animal models. In studies carried out to date, dietary phytic acid reduced the incidence of colonic aberrant crypt foci, putative preneoplastic lesions in rats. Oral administration of phytic acid was shown to inhibit colon carcinogenesis in rodents during the initiation and postinitiation stages. These studies provide evidence for potential chemopreventive properties of phytic acid against colon cancer. With regard to mode of action, phytic acid acts as an antioxidant, to reduce the rate of cell proliferation and to augment the immune response by enhancing the activity of natural killer (NK) cells.*

Cancer of the colon and rectum is the fourth most common cause of cancer deaths worldwide [1]. Cancer of the colon which is one of the leading causes of cancer deaths in both men and women in the Western countries including North America [2] is generally increasing rapidly in Japan including the urban areas of the developing world. Epidemiological studies have demonstrated that increased consumption of fruits and vegetables and high intake of dietary fiber reduce the risk of colon cancer [3]. Interest in the concept of cancer prevention is growing rapidly because the utilization of nutritional factors and naturally-occurring and synthetic agents that can protect against the development and progression of carcinogenic process is not only an attractive but plausible approach to either inhibit or reverse carcinogenesis.

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Key Words: Colon cancer, dietary fiber, phytic acid.

Dietary Fiber and Colon Cancer

The hypothesis that a diet high in fiber may protect against colon cancer was first proposed by Burkitt [4] who observed that African Blacks consuming high fibrous and low-fat foods had lower death rates due to colon cancer compared to their white counterparts eating a low-fiber and high fat diets. Subsequent studies demonstrated that, in populations consuming diets high in total fat, the intake of diets high in total fiber, fibrous foods, and certain whole grain foods reduce risk for colon cancer [5,6]. Intracountry comparisons of dietary fiber and colon cancer mortality rates strongly supported the hypothesis that dietary fiber, especially fiber from cereal sources and pulses, protects against colon cancer [7]. Case-control studies on the relationship between the dietary fiber and colon cancer provided convincing results. Out of 19 case-control studies to assess the role of fiber and fiber-containing foods, 3 studies reported no protective effect, 2 found an increased risk, and 13 studies reported a protective effect of fiber-containing foods and vegetables [8]. Howe *et al* [9] examined the results of combined analysis of 13 case control studies of diet and colon cancer with respect to the intakes of dietary fiber. In this analysis, the individual data records for 5287 colon cancer cases and 10470 control subjects have been pooled for a common analysis which provided substantive evidence that intake of fiber-rich foods is inversely related to colon cancer risk with odds ratios of 1.0, 0.8, 0.7, 0.6, 0.5 for each quintile of consumption from lowest to highest. Similar findings have been reported for a meta-analysis of 16 case-control studies, with odds ratio of 0.6 for the highest versus lowest intake of fiber [3].

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Laboratory animal model studies also indicated that the protective effects of dietary fiber depends on the type of fiber; wheat bran, but neither corn bran nor oat bran, appears to inhibit colon tumor development [10-14]. The effect of dietary wheat bran at 15% level or corn bran plus 5% dietary fat on colon carcinogenesis induced by azoxymethane (AOM) or 3,2'-dimethyl-4-aminobiphenyl (DMBA) was studied in male F344 rats. The composition of diets was adjusted so that all the animals in different experimental groups consumed approximately the same amount of protein, fat, minerals, and vitamins. The animals fed wheat bran had a lower incidence (number of animals with tumors) and multiplicity (number of tumors/animal) of colon tumors than did those fed the control diet whereas corn bran or oat bran had no effect. Thus animal model studies clearly suggest that wheat bran consistently inhibits colon carcinogenesis associated with administration of colon-specific carcinogens.

In human clinical trials, supplements of wheat bran produced a reduction in the incidence of rectal polyps among the individuals genetically predisposed to these lesions [15]. Metabolic epidemiologic studies demonstrated that the individuals consuming high fat and low fiber diets excrete increased levels of fecal mutagens and bile acids compared with those consuming low fat and high fiber or high fat and high fiber diets [16,17]. Additional studies have also provided evidence that wheat-bran supplementation favorably altered a number of biomarkers that are related to the risk of colorectal cancer including fecal mutagenicity [16], fecal secondary bile acids and bacterial 7α-dehydroxylase [17,18] and rectal cell proliferation [19]. Dietary oat bran had no effect on fecal secondary bile acids or 7α-dehydroxylase activity, whereas dietary corn bran increased the levels of secondary bile acids and 7α-dehydroxylase activity. More recent studies have compared the effects of altering both fiber and fat content on fecal secondary bile acids. In this study, healthy subjects who had consumed a typical high fat, low-fiber Western diet and were switched to a low-fat, very-low-fiber diet and then to a low-fat, high-fiber diet showed a dramatic reduction in secondary bile acids during the low-fat and high fiber period, compared with the highfat and low-fiber period. In this connection, several lines of evidence show that dietary fiber affects the metabolic activity of gut microflora; this effect also depends on the type of fiber consumed [17]. There is convincing evidence that these secondary bile acids such as deoxycholic acid and lithocholic acid act as colon tumor promoters. The evidence thus far generated suggests that high dietary fiber including wheat bran reduce the risk of colon cancer.

Inositol Hexaphosphate

Inositol hexaphosphate ($InsP_6$, phytic acid) is a naturally occurring compound found in substantial amounts in cereals and legumes [20]. As discussed above, intake of several classes of foods with high fiber content, and intake of cereals, grains and legumes is inversely associated with colon cancer risk. This finding is significant because cereals, grains and legumes are a rich source of phytic acid. It is possible that one of the mechanisms by which dietary fiber inhibits colon carcinogenesis is through the effects of phytic acid on cell proliferation and differentiation.

Phytic acid and inositol have been tested as chemopreventive agents in *in vitro* systems and laboratory animal models for colon cancer. Sakamoto *et al* [21] investigated the effect of phytic acid on proliferation and differentiation of human cancer cell line, HT-29 *in vitro*. These results showed that phytic acid inhibits cell proliferation and concomitantly increases differentiation suggesting that it suppresses not only the malignant phenotype but also allows the maturation of human colon cancer cells to structurally and behaviorally resemble normal cells. In *in vitro* studies, phytic acid reduced cell proliferation of all human and rodent cell lines tested, including MC-7 human breast carcinoma cells [20]. Enhanced differentiation of cancer cells to the point of reversion back to normal phenotype was also observed in several lines, including the HT-29 human colon carcinoma cell line [2]. These studies provide evidence for many potential beneficial actions of phytic acid.

The exact mechanisms by which phytic acid exert its chemopreventive effects have not been clearly demonstrated. Because of the highly charged nature of phytic acid, it was thought that it could not be transported inside the cell [20]; however, Sakamoto *et al* [2] demonstrated that intragastrically administered [^{3}H]phytic acid was absorbed from the stomach and upper small intestine, distributed into various organs and appeared in the plasma and urine as inositol and inositol P_1, indicating metabolism of the parent compound phytic acid. Phytic acid has been shown to act as an antioxidant, to control cell division and reduce the rate of cell proliferation, and to enhance the activity of natural killer cells, which play an important role in the host defense against neoplasia [20].

Chemopreventive activity of phytic acid has been evaluated in preclinical animal models. Aberrant crypt foci (ACF) are recognized as early preneoplastic lesions in the colon from which adenomas and adenocarcinomas may develop in the colon of both rodents and humans. There is evidence that several inhibitors of ACF formation reduce the incidence of colon tumors in laboratory animal models suggesting that ACF can be used to evaluate novel agents for their potential chemopreventive activities against colon cancer [23]. In this connection, Pretlow *et al* [24] demonstrated that the development of larger ACF with 4 or more aberrant crypt/focus was significantly inhibited in F344 rats administered AOM and given 2% phytic acid in drinking water. Phytic acid at 1 and 2% levels in the diet significantly decreased the number of ACF in the colon [25]. Results also showed that 2% phytic acid administered in combination with 2% green tea extract had a synergistic effect exhibiting a total of about 30% reduction in ACF ($p<0.02$) whereas green tea

extract alone had marginal effect ($p<0.14$). Colon tumor-inhibitory activity of phytic wid has also been evaluated in animal models. Ullah and Shamsuddin [26] showed that administration of 0.1 and 1.0% phytic acid in drinking water significantly inhibited AOM-induced colon tumor incidence, multiplicity and size. Administration of 1% phytic acid in drinking water reduced colon tumor multiplicity by 52% ($p<0.01$), tumor frequency by 56% ($p<0.001$) and tumor size by 62% ($p<0.001$); 0.1% phytic acid exhibited only reduction in tumor size by 71% ($p<0.001$). In another study, the effect of phytic acid administered during the postinitiation stage of colon carcinogenesis was investigated by Shamsuddin and Ullah [27]. Phytic acid when administered in drinking water 2 weeks or 5 months after AOM treatment significantly inhibited colon tumor multiplicity, tumor incidence and tumor size in F344 rats suggesting that the beneficial action of phytic acid is not restricted to the prevention of tumor development but perhaps to treatment of existing tumors as well [27]. In support of these results, Pretlow *et al* [24] have also demonstrated that administration of 2% phytic acid in drinking water during postinitiation stage suppressed AOM-induced colon tumor incidence ($p<0.004$). in F344 rats.

Conclusions

Animal model studies clearly suggest that wheat bran consistently inhibits colon carcinogenesis. Case-control studies show reasonably strong evidence that dietary fiber reduces the risk of colon cancer in humans. Dietary intervention studies provide evidence that wheat bran supplementation decreases the levels of several putative tumor promoters in the colon. Administration of phytic acid, high levels of which are present in wheat bran and other grains inhibits colon carcinogenesis in animal models.

References

1 World Health Organization. The World Heath Report. World Health Organization, Geneva, Switzerland. 1997.

2 Parker SL, Tong T, Bolden S, Wingo PA: Cancer Statistics 1997. A CA Cancer J Clin *47:* 5-27, 1997.

3 Trock B, Lanza E, Greenwald: Dietary fiber, vegetables, and colon canoer: critical review and meta-analyses of the epidemiologic evidence. J Natl Cancer Inst *82:* 650-661, 1990.

4 Burkitt DP: Epidemiology of cancer of the colon and rectum. Cancer *28:* 3-13, 1971.

5 Jensen OM, MacLennan R, Wahrendorf J: Diet, bowel function, fecal characteristics and large bowel cancer in Denmark and Finland. Nutr Cancer *4:* 5-19, 1982.

6 Reddy BS, Sharma C, Simi B, *et al:* Metabolic epidemiology of colon cancer: effect of dietary fiber on fecal mutagens and bile acids in healthy subjects. Cancer Res *47:* 644-648, 1987.

7 McKeown-Eyssen GE, Bright-See E: Dietary factors in colon cancer: international relationships. Nutr Cancer *6:* 160-70, 1984.

8 Pilch SM: Physiological Effects and Health Consequences of Dietary Fiber: Life Sciences Research Office, FASB, Bethesda, MD, 1987.

9 Howe GR, Benito E, Castellato R, *et al:* Dietary intake of fiber and decreased risk of cancers of the colon and rectum evidence from the combined analysis of 13 case-control studies. J Natl Cancer Inst *84:* 1887-1896, 1992.

10 Reddy BS: Nutritional factors and colon cancer. Crit Rev Food Sci Nutr *35:* 175-190, 1995.

11 Watanabe K, Reddy BS, Weisburger JH, Kritchevsky D: Effect of dietary alfalfa, pectin and wheat bran on azoxymethane or methyl-nitrosourea-induced colon carcinogenesis in F344 rats. J Natl Cancer Inst *63:* 151-156, 1979.

12 Reddy BS, Mori H: Effect of dietary wheat bran and dehydrated citrus fiber on 3,2'-dimethyl-4-aminobiphenyl-induced intestinal carcinogenesis in F344 rats. Carcinogenesis *2:* 21-25, 1981.

13 Reddy BS, Mori H, Nicolais M: Effect of dietary wheat bran and dehydrated citrus fiba on azoxymethane-induced intestinal carcinogenesis in F344 rats. J Natl Canca Inst *66:* 553-557, 1981.

14 Reddy BS, Maeura Y, Wayman M: Effect of dietary corn bran and autohydrolyzed lignin on 3,2'-dimethyl-4-aminobiphenyl-induced intestinal carcinogenesis in male Fischa 344 rats. J Natl Cancer Inst *71:* 419-423, 1983.

15 DeCosse J, Mila HEI, Lesser ML: Effect of wheat fiber and vitamins C and E on rectal polyps in patients with familial adenomatous polyposis. J Natl Cancer Inst *81:* 1290-1297, 1989.

16 Reddy B, Engle A, Katsifis S, Simi B, *et al:* Biochemical epidemiology of colon cancer: effect of types of dietary fiber on fecal mutagens, and acid, and neutral sterols in healthy subjects. Cancer Res *49:* 4629-4635, 1989.

17 Reddy BS, Engle A, Simi B, Goldman M: Effect of dietary fiber on colonic bacterial enzymes and bile acids in relation to colon cancer. Gastroenterol *102:* 1475-1482, 1992.

18 Atberts DS, Ritenbaugh C, Story JA, *et al:* Randomized double-blinded, placebo- controlled study of effect of wheat bran fiber and calcium on fecal bile acids in patients with resected adenomatous colon polyps. J Natl Cancer Inst *88:* 81-92 1996.

19 Atberts DS, Einspahr J, Rees McGee S, *et al:* Effects of dietary wheat bran fiber on rectal epithelial cell proliferation in patients with resection for colorectat csncers. J Natl Cancer Inst *82:* 1280-1285, 1990.

20 Shamsuddin AM: Inositol phosphates have novel anticancer function. J Nutr *125:* 725S-732S, 1995.

21 Sakamoto K, Venkatraman G, Shamsuddin AM: Growth inhibition and differentiation of HT-29 celts *in vitro* by inositol hexaphosphate (phytic acid). Carcinogenesis *14:* 1815-1819, 1993.

22 Sakamoto K, Vucenik I, Shamsuddin AM: [^{3}H]Phytic acid (inositol hexaphosphate) is absorbed and distributed to various tissues in rats. J Nutr *123:* 713-720, 1993.

23 Wargovich MH, Chen DD, Jimenez A, *et al:* Aberrant crxpts as a biomarker for colon cancer: evaluation of potential chemopreventive agents in the rat. Cancer Epidemiol Biomarkers Prev *5:* 355-360, 1996.

24 Pretlow TP, O'Riordan MA, Somich GA, Amini SB, Pretlow TG: Aberrant crypts correlate with tumor incidence in F344 rats treated with azoxymethane and phytate. Carcinogenesis *13:* 1509-1512, 1992.

25 Challa A, Rao DR, Reddy BS: Interactive suppression of aberrant crypt foci induced by azoxymethane in rat colon by phytic acid and green tea. Carcinogenesis *18:* 2023-2026, 1997.

26 Ullah A, Shamsuddin AM: Dose-dependent inhibition of large intestinal cancer by inositol hexaphosphate in F344 rats. Carcinogenesis *11:* 2219-2222, 1990.

27 Shamsuddin AM, Ullah A: Inositol hexaphosphate inhibits large intestinal cancer in F344 rats 5 months after induction by azoxymethane. Carcinogenesis *10:* 625-626, 1989.

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EXHIBIT 2

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Diet and Cancer Prevention: The Fiber First Diet©

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Diet can play a major role in cancer prevention. The international differences in cancer incidence are largely accounted for by lifestyle practices that include nutrition, exercise, and alcohol and tobacco use. About 50% of cancer incidence and 35% of cancer mortality in the U.S., represented by cancers of the breast, prostate, pancreas, ovary, endometrium, and colon, are associated with Western dietary habits. Cancer of the stomach, currently a major disease in the Far East, relates to distinct, specific nutritional elements such as excessive salt intake. For these cancers, information is available on possible initiating genotoxic factors, promoting elements, and prophylactic agents. In general, the typical diet in the United States contains low levels of the potent carcinogenic agents, heterocyclic amines, formed during the cooking of meats. It provides only about half the potent appropriate fiber intake and is high in calories. About twice as many calories as would be desirable come from fat, certain kinds of which enhance the development of cancers. Other foods with functional properties, such as soy products and tea, can be beneficial. To achieve reduction in risk of certain cancers, diet must be optimized, primarily to reduce caloric intake and the fat component. The latter should be 20% or less of total caloric intake and fiber should be increased to 25–35 g per day for adults. One approach to achieving these goals is the Fiber First Diet,© a diet designed around adequate fiber intake from grains, especially cereals, vegetables, legumes, and fruits, which thereby reduces both calorie and fat intake. Such dietary improvements will not only reduce cancer and other chronic disease risks, but will contribute to a healthy life to an advanced age. A corollary benefit is a lower cost of medical care.

Key Words: antioxidant; exercise; fat; food; lifestyle; nutrition; vitamins.

For centuries, it has been known that food contains a variety of specific healthful or harmful components. The specific contribution of diet to cancer was highlighted at the beginning of this century in a major treatise on cancer, in which W. R. Williams (1908) concluded, "The incidence of cancer is largely conditioned by nutrition." This insight was extended by a remarkable statistician, E. L. Hoffman (1937), who in an extensive review came to the conclusion that "the underlying cause of cancer is to be found in an excessive intake of foods . . . " Experimental exploration of the relationship of nutrition to cancer began to be pursued in depth, beginning only in the late 1940s and 1950s, with the pioneering work of Tannenbaum (1959). The substantial influence of nutrition on cancer has become increasingly evident, as this group of diseases, together with cardiovascular disease and stroke, have supplanted infectious disease as the most important cause of premature mortality in Western societies. Knowledge of the role of nutrition in the pathogenesis of cancer has continued to accrue (Clifford and Kramer, 1993; Micozzi and Moon, 1992; Miller *et al.*, 1994; Weisburger and Williams, 1995; Williams and Wynder, 1996; World Cancer Research Fund, 1997), with major evidence coming from ecological correlation, particularly between countries such as the U.S. and Japan, where specific cancers differ greatly in incidence. The first food-borne cancer-causing agents to be identified were benzo-[*a*]pyrene and related polycyclic aromatic hydrocarbons, formed during grilling of meats and fishes. It is not known, however, whether the amounts so-formed constitute a human cancer risk upon oral intake. A subsequently discovered food contaminant from fungi, aflatoxin B_1, causes liver cancer in humans, and especially in persons carrying the hepatitis virus (International Agency for Research on Cancer, 1987). In this paper, we review the nutritional and food-borne factors for which substantial evidence exists concerning their influence on cancer incidence. We suggest appropriate actions for cancer reduction through adjustment in dietary practices and adoption of a healthful diet and exercise plan, beginning in childhood.

Diet and Cancer

In 1998, 1,228,600 new cases of cancer, excluding skin cancer, were estimated to have occurred in the United States (Landis *et al.*, 1998). As in our previous reviews (Weisburger and Williams, 1995; Williams and Wynder, 1996), we have estimated the contribution of known etiologic agents on each specific cancer. From the proportion of the total cases represented by that type of cancer, we arrived at an estimate of the contribution of causative agents to cancer incidence. As shown in Table 1, our analysis leads to the conclusion that about 50% of the anticipated cancer incidence and 30–35% of mortality in Americans in 1998 is related to diet and excessive alcohol use. While there are certainly genetic conditions that predispose to cancer (Bradlow *et al.*, 1997), diet and the other major lifestyle factor, smoking, exert a critical influence on cancer risk, in addition to whatever intrinsic susceptibility exists. That is also the case for risk of coronary artery disease.

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TABLE 1
Estimated Causes of Cancer Mortality in the United States, 1998

Type of cause	% of total
Lifestyle cancers	
Diet-related	
High fat, low fiber, low in vegetables and fruits, high in broiled or fried foods: large bowel, breast, pancreas, prostate, ovary, endometrium	30–35
Salted pickled foods, low in vegetables and fruits: stomach[a]	2–3
Tobacco-related: Lung, larynx, oral cavity, bladder, pancreas, kidneys, stomach	30–35
Tobacco and alcohol-related: oral cavity, esophagus	2–3
Alcohol-related: liver, esophagus	1–2
Sunlight-related: melanoma of skin[a]	1–2
Bacteria	
Helicobacter pylori: stomach	1–2
Viruses	2–5
Human papilloma: cervix, penis, anus; hepatitis B, C: liver; HTLV-1: adult T-cell leukemia; Epstein-Barr: B-cell lymphoma	
Lifestyle and occupational exposures	
Tobacco and asbestos, tobacco and mining, tobacco and uranium, tobacco and radium: lung, respiratory tract	2–3
Genetic	2–3
Tumor suppressor gene mutations, including APC, familial adenomatous polyposis: colon; BRCA1, 2: breast; RB1: retinoblastoma; WT 1: Wilms tumor	
Occupational cancers, various carcinogens: bladder and other organs	1
Iatrogenic	1–2
Radiation, drugs: diverse organs, leukemia	
Unknown	3–25[b]

Note. Landis *et al*, 1998. Basal cell and squamous cell cancers of the skin (which account for about 700,00 cases) were excluded from the data.

[a] *Helicobactor pylori* has an interactive role.

[b] This large variation is a function of the broad range calculated for the main diet and tobacco-associated cancers.

Elements in the diet, including both naturally occurring and synthetic components and nutritional factors, can either inhibit or facilitate the oncogenic process (National Research Council, 1996). Dietary elements that facilitate oncogenesis can do so either by initiating the process, usually through genotoxic effects, or enhancing tumor development through epigenetic promotional activity (Williams, 1993a). Information on the contribution of diet constituents to specific cancers, as regards mechanisms of action, are reviewed herein.

A conventional definition of a nutrient is "a substance obtained from food and used in the body to promote growth, maintenance, and/or repair" (Whitney and Hamilton, 1981). The generally recognized broad classes of nutrients are carbohydrates, fats, proteins, vitamins, minerals, and water. Imbalances in nutrients, either inadequacies or excesses, as well as in other food components, are one of the major ways in which diet contributes to cancer etiology (Table 2). The mechanisms and chemicals involved are diverse, involving effects on hormones and other physiological functions, modulation of enzymes, and perturbation of cell kinetics. Ultimately, cancer is the result of a fundamental mutation in cellular DNA and, as will be discussed, diet can convey the genotoxic as well as modulating factors.

Nutritional Inadequacies

One of the most significant nutrient inadequacies in the Western diet is insufficient consumption of fiber. There is no precise definition of fiber, but it may be considered to be the remnants of ingested plant cells that are resistant to digestion by alimentary enzymes (Trowell, 1974). Some of the components of fiber are lignin, cellulose, and hemicellulose. There are soluble and insoluble fibers, both involved in inhibition of cancer risks by specific mechanisms. Fiber has a number of physiologic effects, including its water-holding capacity, which contributes to fecal bulk (Eastwood, 1992).

A protective effect of dietary fiber against colon cancer has been established by numerous negative associations between colon cancer rates and intake of food groups rich in fiber (Freudenheim *et al.*, 1990; Hill, 1998; Howe *et al.*, 1992; Negri *et al.*, 1998; Potter, 1996). The evidence is particularly strong for fiber in cereals and vegetables (Caygil *et al.*, 1998). Some studies do not report an important protective effect of fiber (Fuchs *et al.*, 1999) because of the low intake of cereal fiber. The human data are even less clear for breast cancer (Howe *et al.*, 1990), although several studies have found a protective effect, particularly by cereal fiber and soluble fibers of vegetable origin (Caygil *et al.*, 1998; La Vecchia *et al.*, 1997). In support of the epidemiological observations, animal studies have revealed a protective effect of fiber, particularly of wheat-bran fiber, for colon and breast cancer (Reddy, 1996; Rose,

TABLE 2
Dietary Impacts on Cancer in 1998

Factor	Estimated importance[a]	
	Western communities	Asian/African communities
Nutritional excesses	+++	+[b]
Nutritional inadequacies	+	+
Other dietary inadequacies	++	++
Carcinogens formed in food	++	++
Food contaminants and additives	0	++[c]

[a] O, no impact; +, some impact; ++, strong impact; +++, very strong impact.

[b] In Japan, dietary habits are progressively more Western, and the corresponding cancers are increasing.

[c] Mostly aflatoxin and related mycotoxins, and also traditional high salt use.

1990). The mechanism for the protective effect of fiber against colon cancer involves an increase in stool bulk, thereby diluting fecal bile acids, which are promoters of colon cancer. Other effects may also be involved, such as complexing of bile acids (Klurfeld, 1992; Reddy, 1996).

Low intake of fruits and vegetables, i.e., less than 2 servings per day, has been identified epidemiologically to be associated with risk for cancers of the oral cavity (Takezaki *et al.*, 1996), stomach (Neugut *et al.*, 1996; Trichopoulos *et al.*, 1985), lung (Colditz *et al.*, 1987; Le Marchand, *et al.*, 1989), and breast (Chyou *et al.*, 1990; Trichopoulou *et al.*, 1995). Diets low in fruits and vegetables are, of course, usually low in fiber and high in fat, which may confound the interpretation of associations. Nevertheless, the risks associated with such diets have been attributed to inadequate levels of antioxidants, including vitamin C (ascorbic acid), vitamin A, vitamin E, and carotenoids (Byers and Guerro, 1995; Garewal, 1995; Hwang *et al.*, 1994; Nomura *et al.*, 1997; van Poppel and Goldbohm, 1995; Willett and Hunter, 1994; Zhang *et al.*, 1999), although the evidence is not conclusive (Vainio and Rautalahti, 1999). Nevertheless, it is plausible that Vitamin A could be protective since it influences the differentiation of cells in certain tissues. In addition, the protective effects of carotenoids may relate to their function as precursors of vitamin A, in addition to their antioxidant activity. Some carotenoids, such as lycopene, are superior antioxidants in singlet oxygen quenching. Lycopene is present at high levels in tomatoes, and inadequate consumption could increase some cancer risks (Giovannucci, 1999; Grann *et al.*, 1999; Le Marchand *et al.*, 1989). Importantly, lycopene is well absorbed from tomato juice (Pool-Zobel *et al.*, 1998) or cooked tomato products, with small amounts of olive oil, as typically used in Greece and Italy (Weisburger, 1998c). Vitamin C is an antioxidant and its inhibition of formation of N-nitroso compounds from secondary amines has been postulated to be the basis for its protective effect against stomach cancer (Correa, 1992; Mirvish, 1994). However, its role as a free radical scavenger may be equally important. The normal stomach has an active ascorbic acid secretion mechanism which is impaired by infection with *Helicobacter pylori*, a bacterial agent linked to gastric cancer (De Koster *et al.*, 1994; Hwang *et al.*, 1994). Intake of at least 200 mg/day of vitamin C is desirable. Vegetables and fruits are also rich in flavonoids such as quercitin, which have antioxidant activity (see below).

Although the content of fat in the U.S. diet is high, around 35–40% of calories, intake of certain fatty acids may be suboptimal. Fatty acids as nutrients are metabolically incorporated into glycerolipids and processed into phospholipids, which are components of all cells. They are also oxidized by cyclooxygenase and lipoxygenase to eicosanoids, which are key mediators of biochemical processes, such as prostaglandins. The n-3 polyunsaturated fatty acids have 3 carbons separating the methyl end from the first unsaturated bond and include linolenic (C18:3, n-3), eicosapentanoic acid (C20:5, n-3) and docasahexanoic acid (C22:6, n-3). These have been found to have a protective effect against breast and colon cancer (Carroll, 1992; Cave, 1996; Singh *et al.*, 1997). Also, the growth and metastasis of a transplantable human breast tumor in a mouse model system was suppressed by high levels of n-3 fatty acids, but enhanced by n-6-polyunsaturated oils (Rose and Connolly, 1993). The protective mechanisms might involve a metabolic effect (Sardesai, 1992) such as increased biosynthesis of the 3-series prostaglandins (PGE_3) and thromboxanes (TXA_3). These compete with the 2-series compounds, which are biologically active as cancer promoters. Also, n-3 fatty acids inhibit the synthesis of arachidonic acid from linoleic acid, and compete with arachidonic acid as a substrate for cyclooxygenase. In addition, fatty acids are ligands for the peroxisome proliferator-activated receptors (PPARs) (Krey *et al.*, 1997), which are gene transcription factors belonging to the nuclear hormone receptor superfamily.

Deficiencies in specific micronutrients have been related to increases in several cancers under certain circumstances. Imbalances in dietary iodine intake can, to some extent, be the basis for geographic differences in thyroid cancer (Franceschi *et al.*, 1993). The minerals calcium and selenium are anticarcinogenic in animal models, especially as regards the large intestine. Calcium lowers the rate of cell cycling, particularly in the intestinal tract (Lipkin and Newmark, 1995). Several epidemiological studies have found an inverse association between calcium intake and the risk of colorectal cancer (Garland *et al.*, 1985), but not in all (Martinez and Willett, 1998). In addition, calcium is important for other aspects of good health, such as bone strength. Some epidemiological studies suggest that vitamin D intake is inversely associated with colon cancer risk (Martinez and Willett, 1998), but the data are sparse. Such a protective effect could stem from an action on absorption and metabolism of calcium.

Asian countries historically have had low rates of breast, colon, and prostate cancers, which was largely attributable to low-fat diets (see Nutritional Excesses). Current dietary habits in Japan are changing to a Western pattern, with concomitant increase in Western-type cancers (Tominaga and Kuroishi, 1997). These findings provide strong evidence for an association of the Western dietary pattern with the types of cancers frequent in North America. In addition, the traditional diets in Far Eastern countries are comprised of many soy products. These are rich in isoflavones (Fournier *et al.*, 1998; McLaughlin *et al.*, 1995) such as genistein, a functional agent with anticarcinogenic properties, which has been observed in experimental models (see below). Typical Western diets are quite low in isoflavones, and hence, this may constitute a suboptimal condition that could also develop in Asian countries as a shift to Western-type diets progresses.

Nutritional Excesses

Over-nutrition is well established as a cause of increased risk for a number of cancers (Kritchevsky, 1995). This has been

corroborated in animal models (Pariza and Boutwell, 1987) in which caloric restriction strongly inhibits carcinogenesis. For some cancers, as will be discussed, the contribution of overnutrition relates to specific dietary excesses, while for others such as renal cell cancer (Wolk *et al.*, 1996), a general energy effect appears to be involved. Also, obesity, which reflects excess energy intake, is associated with greater risk for endometrial neoplasia (Schottenfeld, 1995).

In the United States, fat intake from both plant and animal sources averages about 100 g/day for males and 60g/day for females, accounting for about 35% of total energy (Rolls and Hill, 1998). About 25% of this is contributed by animal products, which are high in saturated fatty acids (Grundy, 1996; Micozzi and Moon, 1992). Substantial evidence is available that excess consumption of total calories or specific food components creates a condition of metabolic overload that leads to increases in cancer (Kritchevsky, 1995; Williams and Wynder, 1996; Wynder and Williams, 1993). In population or ecological studies, high-fat intake is strongly associated with an increased prevalence of colon cancer (Potter *et al.*, 1993), breast cancer (Boyd *et al.*, 1993; Carroll, 1992), and, possibly, cancer of the prostate (Mettlin, 1997) and lung (Swanson *et al.*, 1997). This relationship is sometimes (Hayes *et al.*, 1999), but not always, evident in cohort or case-control studies (Kampman *et al.*, 1999; Martin-Moreno *et al.*, 1994), the latter perhaps because even the lowest intake group is also overexposed (i.e., >25% calories from fat) in populations with traditional high fat consumption. Nevertheless, case-control studies generally support a positive association for saturated or animal fat intake and breast cancer in postmenopausal women (Howe, 1994). Importantly, the rates in postmenopausal women differ most between countries of high and low fat intake. The amount of fat intake may affect serum estradiol levels (Wu *et al*, 1999). For prostate cancer risk, case-control studies support an association of greater intake of dietary fat, especially saturated fat, whereas all cohort studies have not shown consistency (Nomura and Kolonel, 1991), although some do provide support (Le Marchand *et al.*, 1994). Likewise, increased risk for pancreas cancer has been linked to high-fat intake (Lyon *et al.*, 1993), particularly via meat consumption (Gold and Goldin, 1998; Howe and Burch, 1996; Soler *et al.*, 1998). Studies in animal models generally demonstrate that fat influences cancer development in the breast (Welsch, 1992), colon (Reddy, 1996), and pancreas (Birt *et al.*, 1989), although specific exceptions have been observed. Less experimental evidence is available for prostate cancer, perhaps in part because a good laboratory model to investigate dietary modulation of prostate cancer is not available. The enhancing effects of high-fat diets have been attributed to increased caloric intake, which certainly increases tumor development (Keenan *et al.*, 1997), but analysis of the collective literature reveals an enhancing effect by specific dietary fats (Freedman *et al.*, 1990) as well as a general effect from excessive calories (Birt *et al.*, 1989).

One element in the role of high fat intake appears to be in levels of certain fatty acids. In contrast to the low levels of n-3 fatty acids previously discussed, most plant oils are high in n-6 fatty acids such as linoleic acid (C18: 2nB6), which is positively associated with prostate, breast (postmenopausal), colon (distal), and pancreatic cancer risk (Godley *et al.*, 1996; Micozzi and Moon, 1992). In rodent models, n-6 polyunsaturated oils are stronger promoters than monounsaturated oils, such as olive oil, or n-3 polyunsaturated oils (Carroll, 1992; Cave, 1996), yet, they all provide an identical caloric load. The mechanisms of action of specific oils as regards biosynthesis and degradation of bile acids or estrogen are distinct, and parallel their enhancing action, or lack thereof. Corresponding to the experimental findings, the rates of breast and colon cancer in Mediterranean countries with a high intake of olive oil are appreciably lower than in North America or the United Kingdom (Martin-Moreno *et al.* 1994; Trichopoulou *et al.*, 1995). A further contributing element in the Mediterranean region, however, might be the high intake of vegetables and tomatoes, with protective actions, as discussed above.

Nevertheless, caloric intake and possibly nutrient density may be of importance in humans, especially where overnutrition leads to obesity. It is noteworthy that in animal models, the only modulation of diet that consistently maintains maximal longevity is caloric restriction (Masoro, 1991). In part, this is due to an effect on cell cycling, itself a key factor in carcinogenesis and longevity. No conclusive association, however, has been established between sugar intake and any cancer (Burley 1997, 1998).

Excess salting of foods has been associated with increased risk of stomach cancer (Hwang *et al.*, 1994; Kneller *et al.*, 1992), for which laboratory studies provide support (Chen *et al.*, 1996; Sugimura, 1996; Takahashi *et al.*, 1983). Similar considerations may hold for cancer of the esophagus in China.

Thus, overall, there is strong evidence that nutritional excesses have a significant impact on the occurrence of a number of important types of cancer in Western societies and others (Table 2), as was concluded by W. R. Williams as long ago as 1908. There is also evidence for a role of exercise in reducing cancer risk (Friedenreich and Rohan, 1995), which may relate to diet.

Cancer-Modulating Food Components

Chemicals with carcinogenic activity in animals can be present in food through several different sources (Table 3). These include carcinogens of the type that have the ability to react with DNA and hence are mutagenic, and those that are not chemically reactive but produce other epigenetic cellular effects which bear on cancer development (Williams and Weisburger, 1991).

Food-borne carcinogenic chemicals can be detected by a variety of highly sensitive analytical techniques, and generally, such exposures are currently held to very low levels. Aflatoxins, which are potent carcinogenic mycotoxins produced by

TABLE 3
Sources of Detectable Laboratory Carcinogens in Food

Source	Example
Naturally occurring	
Plant	Cycasin
Microbial	Mycotoxins
Contaminant	
Introduced before processing	DDT
Introduced during processing	Trichloroethylene, methylene chloride
Additive	Butylated hydroxyanisole, saccharin
Formed from food components	
During processing	Nitrosamides/nitrosamines
During cooking	Benzo(a)pyrene and related hydrocarbons, heterocyclic amines
In the body	Nitrosamides/nitrosamines

Note. Many of the agents listed are detectable only at minute levels (i.e., <1 ppm) by highly sensitive analytical techniques.

fungi, were not discovered until 1960, but probably were at significant levels in certain crops such as corn or peanuts prior to that time (Williams, 1994). Aflatoxin has been associated with liver cancer in Asian and African countries, where exposure is high, and chronic hepatitis contributes also. In the United States, reduced mycotoxin exposure, subsequent to its recognition, and/or increased anticarcinogens in the diet, may be speculated to underlie the decline in liver cancer deaths (Williams, 1994). They have diminished from about 12 per 100,000 in males in 1930 to about 5 per 100,000 in 1990 (Landis *et al.*, 1998). Also in the past, nitrate (saltpeter) and salt were used at high levels for food preservation (Jones, 1992), and these may have contributed to the formation of carcinogens suspected to have been involved in the high incidence of stomach cancer prevalent in the early part of this century (Chen *et al.*, 1996; Correa, 1992; Howson *et al.*, 1986; Weisburger and Williams, 1995). However, the evidence has been considered inconclusive (Eichholzer and Gutzwiller, 1998).

A large number of substances that produce liver tumors in rodents, such as organochlorine pesticides, have been present at trace levels in food since their introduction in the 1940s for agricultural use. Obviously, these have not led to an increase in human liver cancer in the U.S., since, as noted, this cancer has declined over the past 50 years.

During the cooking of food, a variety of heterocyclic amines is formed in the browning reaction (Adamson *et al.*, 1995; Felton and Gentile, 1997; Weisburger *et al.*, 1998). Prominent among these is 2-amino-1-methyl-6-phenylimidazo{4,5-b}pyridine (PhIP). These DNA-reactive agents are potent multiorgan and multispecies carcinogens, including in primates. It has been postulated that they may be the initiating agents for breast, prostate, pancreas, and colon cancers in Western societies (Weisburger and Williams, 1995), with PhIP estimated to account for half of the incremental cancer risk (Layton *et al.*, 1995). Recently, consumption of well done red meat, a source of heterocyclic amines, has been associated with an increased risk of colorectal adenomas, precursors of carcinomas (Sinha *et al.*, 1999)

In the stomach, nitrosation reactions involving nitrates and other components in the diet give rise to nitrosamides and nitrosamines These carcinogens are postulated to be the initiating agents for stomach and esophageal cancer (Correa, 1992; Craddock, 1992), a concept which is supported by the demonstration that certain nitroso compounds induce gastric and esophageal cancer in rodents (Correa, 1992; Craddock, 1992; Mirvish, 1994). A novel direct-acting mutagen, 2-chloro-4-methylbutanoic acid and possible carcinogen for the stomach, was isolated from fish preserved with salt and saltpeter (Chen *et al.*, 1996; Furihata *et al.*, 1996).

Food also can be the source of infectious agents, such as the hepatitis B virus in shellfish and liver flukes in raw fish, which cause chronic tissue injury leading to increases in specific cancers.

Among beverages, alcohol consumed in excessive amounts is clearly associated with liver disease and increased risk of liver cancer, as well as esophageal cancer in association with cigarette smoking (International Agency for Research on Cancer, 1988). Weak and inconsistent positive associations between alcohol consumption and breast cancer have been reported in many epidemiologic studies (Rosenberg *et al.*, 1993), and current observations continue to show weak or absent association (Freudenheim *et al.*, 1995; Holmberg *et al.*, 1995; Longnecker *et al.*, 1995). Increased risk of cancer of the colon is also reported to be associated with alcohol consumption (Kune and Vatetta, 1992; Le Marchand *et al.*, 1997). Also, rectal cancer may be associated with alcohol intake, and metabolism to acetaldehyde has been postulated (Seitz, 1990). These epidemiological observations have not been corroborated in experimental studies and no mechanism has been elucidated. Coffee has also been discussed as a risk factor, particularly for bladder cancer, but a causal association has not been established (International Agency for Research on Cancer, 1991). In fact, caffeine may possibly be antimutagenic (Weisburger, *et al.*, 1998). As discussed below, tea appears to be anticarcinogenic.

Although several synthetic food additives are established experimental carcinogens when administered chronically at high doses, none has been associated with cancer in humans (Williams and Weisburger, 1991). To the contrary, antioxidants such as butylated hydroxyanisole and butylated hydroxytoluene may be functioning as anticarcinogens in the diet (Williams, 1993b, 1994). Generally, carcinogenic agents are not allowed as food additives. However, saccharin, a well-documented rodent bladder carcinogen at high dietary levels, operating through an epigenetic mechanism with a sharp dose-response displaying a no-effect threshold (Whysner and Williams, 1996), has been permitted as an exception. Its unrestricted use for many decades has pro-

TABLE 4
Food-Borne Inhibitors of Experimental Cancer

Food component	Food	Experimental cancer inhibited
Bifidobacterium longum cultures	Fermented dairy products	Large intestine, liver
Calcium	Dairy products	Large intestine
Carotenoids, β-carotene	Green/yellow vegetables, fruits	Large intestine, stomach
Conjugated linoleic acid	Cheese, cooked meats, oils(?)	Breast, forestomach, skin
Diallyl sulfide	Garlic, onions	Esophagus, forestomach, large intestine, liver
Fiber	Bran cereal and bread, vegetables	Breast, large intestine, pancreas
Fructans	Chicory, garlic, onion, asparagus	Large intestine
Indole-3-carbinol (glucobrassicin)	Cruciferous vegetables	Breast, endometrium, forestomach, liver, lung
Minerals		
Calcium	Dairy products	Large intestine, breast
Selenium	Vegetables, meat	Breast, skin, large intestine, liver, lung
Monoterpenes		
D-carvone	Caraway seed	Forestomach, lung
D-limonene	Citrus fruits	Breast, forestomach, lung
Myoinositol (phytate)	Bran cereals and bread	Large intestine, breast
Phenolics (glycosides)		
Catechins	Fruits, vegetables	Large intestine, breast
(-)-epigallocatechin-3-gallate	Tea	Lung, esophagus, skin, breast, small and large intestine
Flavonoids	Vegetables	
Quercetin	Vegetables	Breast, large intestine
Naringenin	Citrus	Breast
Isoflavones	Soy products	Breast, large intestine
Genistein		
Hydroxycinnamic acids	Fruits, vegetables,	Forestomach
Caffeic acid	Soy, cereals	
Chlorogenic acid		Large intestine, liver
Ferulic acid		Forestomach
Tannins	Vegetables	Forestomach, lung
Tannic acid		
Ellagic acid	Fruits	Esophagus, liver, skin
Protease inhibitors		
Bowman-Birk	Soy	Liver
Edi ProA soy protein	Soy	Liver
Soy protein isolate	Soy	Breast, large intestine
Thiocyanates (glucosinolates):	Broccoli, cabbage	Breast, forestomach
Benzyl isothiocyanate	Watercress	Liver, lung
Benzyl thiocyanate		Breast, liver
Phenethyl isothiocyanate		Breast, esophagus, forestomach, lung
Sulforaphane	Broccoli	Breast, large intestine
Vitamins		
Vitamin A	Liver, milk, eggs, vegetables	Liver, lung
Vitamin C (ascorbic acid)	Citrus fruits, vegetables	Kidney, large intestine, lung, stomach
Vitamin E (α-tocopherol)[a]	Seeds, nuts, vegetable and seed oils	Breast, forestomach, large intestine, oral, skin

[a] Foods listed do not provide optimal amounts, and supplementation with 100–200 international units, with the main meal of the day is suggested.

vided evidence that the cancer risks from epigenetic agents are negligible under actual, realistic conditions of use. Nevertheless, one natural food "additive," salt, when used in excess, appears to play a role in stomach cancer (Chen *et al.*, 1996; Kneller *et al.*, 1992; Takahashi *et al.*, 1983). This indicates that high-level exposures to some agents can enhance risk. High salt intake also relates to hypertension. Low consumption of some of these protective components is associated with increased cancer risks, as discussed in Nutritional Inadequacies.

Foods also contain a variety of components that have been demonstrated in animal models to inhibit specific chemical-induced cancers (Table 4). These agents can function as carcinogen-reducing agents, reducing formation or absorption of carcinogens; carcinogenesis-blocking agents, blocking carcinogen reactions with cellular macromolecules; or cancer-suppressing agents, suppressing neoplastic development. Low consumption of some of these protective components is associated with increased cancer risks, as discussed in Nutritional Inadequacies.

TABLE 5
Food-Borne Agents That Influence Human Cancers

Cancer	DNA-reactive carcinogen	Enhancing or promoting factor	Protective factor
Breast	Heterocyclic amines	High-fat diet[a]	Adequate fiber, soy, tea, ?calcium, ?vitamin D
Prostate	?Heterocyclic amines	High fat diet[a]	Soy, lycopene, cooked tomatoes
Lung	(Tobacco smoke)[a]	?High fat diet[a]	Fruits and vegetables, soy, tea
	(Occupational exposures)	(Tobacco smoke)	
Large intestine	Heterocyclic amines	High fat diet[a]	Adequate fiber, calcium, vitamin D, soy, tea
Pancreas	(Tobacco smoke)	?High fat, meat diet	Soy, tea
	?Heterocyclic amines		?vegetables and fruits
Stomach	?Reactive chloro- or nitroso- compounds	High intake of salted and preserved foods (also *Helicobacter pylori*)	Fruits and vegetables, soy, tea
Liver	Aflatoxins	Alcohol (hepatitis)	
Esophagus	?Nitrosamines	Alcohol	Tea, ?soy
	(Tobacco smoke)		

Note. Agents in parentheses are not food-borne.
[a] Monounsaturated oils, olive or canola oils, do not promote; n-3-polyunsaturated oils are protective.

Specific Human Cancers Influenced by Food-Borne Components

Patterns of food consumption are well established as being associated with incidences of certain cancers, as discussed above, and foods have been documented to contain cancer-modulating agents from a variety of sources (Weisburger, 1998b). The contribution to the main human cancers of specific carcinogens, enhancing or inhibiting factors conveyed in food, is summarized in Table 5. These agents in aggregate account for the 50% of cancer attributable to diet (Table 1).

The potential for modification of diet to determine cancer rates is illustrated strikingly by the decline of stomach cancer in most populations (Correa and Chen, 1994; Howson *et al.*, 1986). Stomach cancer rates in the United States have decreased from about 38 deaths per 100,000 males in 1930 to about 6 per 100,000 in 1990, and from about 28 deaths per 100,000 females to about 4 per 100,000 (Landis *et al.*, 1998). A consistent factor associated with reduced risk was intake of vegetables and fruit (Boeing, 1991, postulated to provide protective vitamin C and β-carotene (Hansson *et al.*, 1994; Steinmetz and Potter, 1991). As described above, vitamin C may inhibit the nitrosation reaction in the stomach that leads to carcinogen formation. Another possible contributor to this dramatic decline is changes in methods of food preservation. The use of salting and nitrates has diminished (Hwang *et al.*, 1994; Weisburger, 1998b; Weisburger and Williams, 1995) in favor of canning, freezing, and refrigeration. Salt and nitrates provide substrates for the formation of carcinogens, and salt is a promoter of stomach cancer in animal models. Thus, reduction of these elements could lessen carcinogenic effects in the stomach.

Another cancer that has declined in the United States in both genders is liver cancer (Landis *et al.*, 1998). This reduction has occurred in spite of increased exposures to food-borne animal liver carcinogens such as organochlorine pesticides. As noted above, one genotoxic liver carcinogen that has been carefully controlled over the past 30 years is aflatoxin, a major contributor to liver cancer in parts of the world with high contamination, and hence this reduction may be in part responsible for the decline. Regardless of the basis for the decline of stomach and liver cancers, their reduction clearly demonstrates that specific cancers can be reduced through effective prophylaxis. The current knowledge of the role of nutrition and other food components in the etiology of major cancers such as colon, breast, pancreas, and prostate (Table 4) offers an attractive opportunity for cancer control.

Strategies for Cancer Prophylaxis

Nutrition

Cancer prevention must focus, beginning in childhood, on managerial approaches to assuring optimal nutrition and balance of food components (Williams, C. L., 1996; Williams, C. L. *et al.*, 1993), since cancer is a "chronic" condition that develops over a long period of time, and certain cancers may have their inception during childhood. In addition, food preferences are established in childhood. As a general guide, an attainable goal after adolescence is a diet comprising 25% *or less* of calories from fat (no more than 40 g per day for an adult) and 25–35 g of fiber (Wynder *et al.*, 1992; Williams and Wynder, 1996). For children, fat consumption after the age of 2 should also be no more than 30% of calories consumed (range 20–30%), and an adequate total fiber intake in g per day should follow the "age plus 5" formula, eventually reaching the minimally desirable adult level of 25g/day by age 20 (Williams, C. L. *et al.*, 1995). A balanced diet should consist of 6 or more servings per day from the grain group (whole grain bread, cereal, rice, and pasta items), 3–5 servings of green and yellow vegetables, 2–4 servings of fruits, and 2 or 3 servings of low-fat or fat-free dairy products, as recommended by

TABLE 6
Fiber First Diet©

Dietary fiber intake per day
2–19 years old, age + 5 in g
≥ 20 years old, 25–35g
50% from grains
30% from vegetables and legumes
20% from fruits
Fluid intake per day: 8–12 glasses (8-ounce)

various authorities (Dwyer, 1993). Whole-grain products are an excellent source of insoluble fiber (Jacobs *et al.*, 1998). As an animal protein source, fish is preferable, because of its content of protective n-3 fatty acids and might be consumed 3 or more times per week. Meat and poultry should be limited to 2–3 small servings, preferably low fat versions, per week. These foods will deliver the desirable daily intakes of 200 mg of vitamin C, 400 units of vitamin D, and 1.0–1.5 g of calcium, which Lachance (1994) proposes as an appropriate Recommended Daily Allowance based upon an "ideal" content. A well-balanced diet should not require supplementation, except perhaps for vitamin E, which is delivered at only about 25 IU in recommended diets. Daily use of multivitamins has been reported to be associated with reduced colon cancer risk (White *et al.*, 1997) although evidence for anticancer activity has not been established (Byers and Guerro, 1995; Greenberg *et al.*, 1994). Nevertheless, use of a multivitamin with at least 200 IU of vitamin E is recommended for reduction of risk of cardiovascular disease. These dietary recommendations will also provide reduced risk for other major diseases, particularly coronary heart disease and stroke (Shils *et al.*, 1994; Sugimura, 1996; Weisburger, 1998b; Weisburger and Williams, 1995; Willett, 1994), and certainly are not expected to do harm.

To achieve these goals, an attractive approach is the Fiber First Diet© (FFD) (Table 6), which emphasizes that fiber be consumed first in the day and first in each meal. The desirable fiber intake for adults is 25–35 g/day. For children, minimal intake is achieved by the "age plus 5" principle, i.e., the g per day is calculated by adding 5 to the child=s age (Williams, 1995a,b; Williams and Bollella, 1995). This results in a progressive intake to age 20 when the adult goal is reached. A healthy range of dietary-fiber intake for children is age + 5 to age + 10 grams per day. The source of fiber should be approximately 50% from grains, including wheat bran, 30% from vegetables and legumes, and 20% from fruits (Fig. 1). This must be accompanied by adequate water and fluid intake to hydrate the fiber in the gut. A desirable source of fluid is fruit and vegetable juices, which, respectively, are sources of bioavailable vitamin C (Weber *et al.*, 1996) and β-carotene or lycopene (Pool-Zobel *et al.*, 1998). These, like tea, discussed below, provide valuable functional effects.

The basic elements of the FFD are given in Table 7, and a comparison with typical meals is provided in Table 8. Most

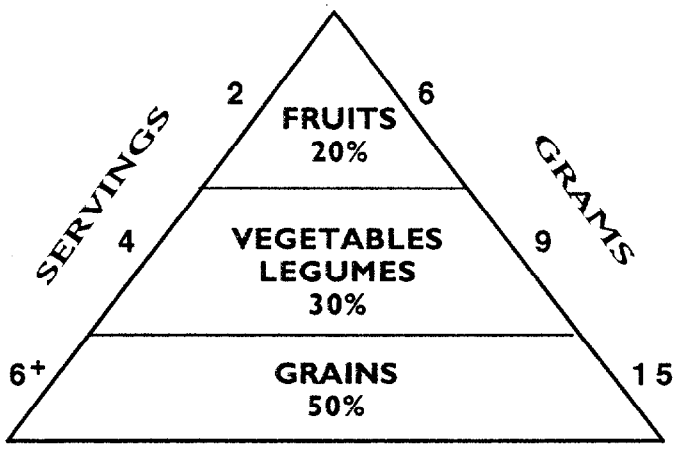

FIG. 1. Adult fiber pyramid.

individuals will be able to achieve the fiber-first diet by consuming a high-fiber breakfast cereal, using whole wheat bread in a sandwich at lunchtime, and consuming 3 to 5 vegetables and 2 fruits throughout each day. In addition to providing adequate fiber and displacing fat in the diet, key components of the FFD (grains, vegetables, legumes, and fruit) furnish important vitamins and minerals. In addition, the FFD provides other functional components that have been associated with reduced cancer risk (Steinmetz and Potter, 1991), discussed below. The FFD should slightly

TABLE 7
Guidelines for Dietary Fiber Intake on Fiber First Diet©

Adult[a]	Child[b]
Breakfast	Breakfast
Wheat bran cereal[c] (8 g)	2 cup wheat bran cereal[c] (4 g)
1 fruit (4 g)	2 fruit (2 g)
1 slice whole wheat toast (2 g)	
Lunch[c]	Lunch[c]
2 slices whole wheat bread[d] (4 g)	2 slices whole wheat bread[d] (4 g)
1 fruit (3 g)	1 fruit (3 g)
	Snack
	1/2 cup fruit (2 g)
Dinner[e]	Dinner[c,e]
1 cup vegetable or legume (4 g)	1/4 cup vegetable or legume (1 g)
1 baked potato w/skin (4 g)	1 baked potato– no skin (2 g)
2 tomato (1 g)	2 cup fruit (2 g)
1 cup lettuce (1 g)	
Total dietary fiber = 31 grams	Total dietary fiber = 20 grams

Note. The listed foods are fiber-containing foods which would be chosen "first" to achieve fiber goal. Other foods and drinks would accompany these to complete dietary requirements.

[a] Adult recommendation for dietary fiber: 25–35 grams per day.

[b] Child, age 10 (recommended range of fiber intake based on age + 5 to 10 guideline = 15–20 g/day).

[c] Include a cup of low fat milk.

[d] Bread as part of a sandwich.

[e] Dinner would also include a serving of lean meat, fish or other source of protein.

TABLE 8
Fiber First Diet© Versus Usual U.S. Diet

Typical U.S. diet 13 g fiber; 1950 calories 34% energy from fat					Fiber First Diet© 31.5 g fiber; 1800 calories 24% energy from fat				
Meal	Fiber (g)	Fat (g)	KCAL	Calcium (mg)	Meal	Fiber (g)	Fat (g)	KCAL	Calcium (mg)
Breakfast:					Breakfast:				
1 corn muffin (1½ oz.)	1	5	125		1 cup Raisin Bran	8	1.5	200	
1 tsp. butter	0	5	45		1 cup strawberries, fresh	3.5	0	40	
1 cup beverage[a]	0	0	5		1 cup milk, 1%	0	2.5	100	300
1 tbsp. half and half	0	2	20						
Lunch:					Lunch:				
1 cheeseburger	2	14	310	200	2 oz turkey breast	0	2	70	
1 small French fries	2	12	220		2 slices whole wheat bread	4	2	160	
1 small choc. shake	0	5	350	581	1 tbsp lite mayo	0	5	45	
					½ large tomato	1	0	25	
					1 cup garden salad	2	0	25	
					1 tsp. olive oil + vinegar	0	5	45	
					seltzer with lemon	0	0	0	
					1 apple, small	3	0	60	
Snack:					Snack:				
banana	4	0	120		1 Nutrigrain bar[c]	1	3	140	200
					1 cup milk, 1%	0	2.5	100	300
Dinner:					Dinner:				
salad: 1 cup iceburg lettuce	1	0	25		3 oz. broiled salmon	0	9	165	
½ large tomato	1	0	25		½ cup broccoli sauteed	2	0	25	
2 tbsp regular dressing	0	10	90		with 1 tsp. olive oil + garlic	0	5	45	
1½ cup white rice	2	0	240		6 oz. baked potato + skin	4	1	180	
3 oz. fried chicken[b]	0	15	225		3 tbsp. low-fat sour cream	0	5	45	50
1 cup regular soda	0	0	150		1 cup milk, 1% fat	0	2.5	100	300
					Snack:				
					½ cup peaches, fresh	2	0	60	
					½ cup frozen yogurt	0	0	90	450
					3 graham crackers, (2½ in. squares)	1	2	80	
DAILY TOTALS	13	68	1950	781		31.5	48	1800	1600

[a] Tea, coffee.
[b] All white-meat, no skin.
[c] Kellogg.

reduce daily energy intake (Table 8), especially since consumption of high-fiber foods reduces food intake at the next meal (Rolls and Hill, 1998). While adoption of the FFD will usually lower fat intake, wherever possible, reduced fat products such as skim milk should be used. Snacks, especially, should be low in fat. Fruits make wholesome, tasty between-meal snacks. Even potato chips are available in low-fat versions, prepared by baking or frying in non-digestible fat substitutes such as olean.

Functional Foods

In addition to the importance of nutrition in cancer prevention, recognition is growing that foods contain components that have specific effects on genomic, cellular, biochemical, or physiological function, which can protect against disease processes, including cancer and cardiovascular disease. Epidemiological studies reveal that reduced risk of some cancers is associated with consumption of foods such as vegetables (Block *et al.*, 1992), whole grain cereals and breads (Caygill *et al.*, 1998), and soy products (Fournier *et al.*, 1998; Mclaughlin *et al.*, 1995). Specific constituents of these foods that are believed to be responsible for the protective effects have been identified. Those food components that have been demonstrated to have anticarcinogenic effects in experimental systems are listed in Table 5. Among these are phenolics, which occur usually as glycosides in a wide array of foods; carotenoids; phytoestrogens; and minor nutrients such as minerals and vitamins (Wattenberg, 1992). Foods rich in such components have been referred to as "functional foods."

Prominent among functional components of food are antioxidants (Aruoma, 1994). The antioxidants in whole grains have been suggested as contributors to the anticarcinogenicity of these foods (Johnson, 1998), in addition to their fiber effect. An important type of antioxidant in plants is polyphenols, which have properties similar to the synthetic antioxidant phenolics BHA and BHT. The polyphenols present in tea have exhibited anticarcinogenic activity in experimental models (Katiyar and Mukhtar, 1996; Weisburger, 1997b, 1998a; Yang and Wang, 1993) (Table 4). In addition to its antioxidant content, tea is, of course, mainly water, which is an important essential nutrient. Epidemiological studies have not yet yielded strong evidence of cancer risk reduction. However, green-tea drinking in China and Japan is associated with lower rates of esophageal and gastric cancers, which are highly prevalent in these countries, and also of pancreatic, colorectal, and bladder cancers (reviewed by Blot *et al.*, 1996, and Bushman, 1998). Laboratory research showed that green and black teas have similar protective properties as antimutagens and anticarcinogens (Weisburger, 1998a). The known underlying mechanisms, therefore, suggest that tea should be health promoting. Also, several epidemiological studies on tea use have noted a reduced mortality from heart disease, with similar risk factors to those related to the nutritionally-linked cancers. Cocoa is another plant source of polyphenols (Zumbé, 1998). Antioxidants such as polyphenols and flavonoids (Williamson *et al.*, 1998) are also free-radical scavengers, and this activity may be involved in their anticarcinogenicity (Aruoma, 1994).

Carotenoids comprise about 600 pigmented chemicals formed in plants. Some have activity as provitamin A, and most have some antioxidant potential. The association of reduced cancer risks with consumption of fruits and vegetables has been attributed to carotenoids, particularly β-carotene, which has shown anticancer activity in animal models (Toma *et al.*, 1995).

Over 90 plants have been identified as possessing some estrogenic activity (Farnsworth *et al.*, 1975) due to their content of phytoestrogens, which include isoflavones, coumestans, and lignans (Kurzer and Xu, 1997; Reinli and Block 1996). Epidemiologic studies suggest reduced risks of prostate and gastric cancers with consumption of soy foods (Adlercreutz *et al.*, 1993; Fournier *et al.*, 1998), which are the richest dietary source of isoflavones, and include the aglycones: genistein, daidzein, and glycitein. In animal studies, genistein has been reported to inhibit mammary carcinogenesis in rats, but this has not been substantiated, and the biologic properties appear to be quite complex (Barnes, 1997). Oilseeds, such as flaxseed, are the richest plant sources of lignans, such as secoisolariciresinol.

Plants belonging to the genus *Allium* include garlic, onion, leek, and shallot, which contain large amounts of organosulfur compounds, as well as glutathione and flavonols. *Allium* vegetable consumption has been associated, in case-control studies, with reduced cancer risk (Steinmetz and Potter, 1991), although this was not confirmed for lung cancer in a prospective cohort study (Dorant *et al.*, 1994).

Another category of functional foods consists of prebiotics that stimulate the growth in the gut and/or activity of types of bacteria, such as *Lactobacillus acidophilus* and *Bifidobacterium* species, which are beneficial (Gibson and Roberfroid, 1995). The β (2–1)D fructans, inulin and oligofructose, are soluble fibers that are fermented by colonic microflora and stimulate the growth of bifidobacteria. These fructans inhibited the induction of preneoplastic lesions in rat colon (Reddy *et al.*, 1997). Foods such as yogurt are considered probiotics because they contain the beneficial live microbes. While several studies have shown that administration of bifidobacteria or lactobacilli to carcinogen-exposed animals reduced colon preneoplastic or neoplastic lesions, results have not been consistent (Gallaher *et al.*, 1996).

In order for functional components to produce a biological effect, they must, of course, be bioavailable in sufficient amounts. The richest sources of vitamin E are vegetable oils (Sokol, 1996), but since these should be limited in the diet, supplementation is the only practical way to achieve sufficient intake. Vitamin E, and the other fat-soluble vitamins A and D, must be consumed as part of a fat-containing meal to be absorbed. Other components, such as quercitin (Gugler *et al.*, 1975), also are not well absorbed.

Intervention trials are currently underway, in which some of these functional food components, such as β-carotene and vitamin A, are being administered as supplements to various study populations (Boone *et al.*, 1997; Greenwald *et al.*, 1995). Some early results have been disappointing (Vainio and Rautalahti, 1998), and it would be remarkable if change in single minor components of diet could alter the risk of a major cancer, such as lung cancer due to continuing smoking that provides an overpowering carcinogenic stimulus. In fact, the trials with β-carotene have shown increases in lung cancer (The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group, 1994; Omenn *et al.*, 1996). As discussed by Olson (1996), antioxidants in some situations can exert prooxidant effects, and large doses of β-carotene can inhibit the absorption of other carotenoids, leading to nutritional imbalances.

Synthetic chemicals with functional properties superior to those of natural food components are also available. These include antioxidants such as butylated hydroxyanisole and butylated hydroxytoluene, isothiocyanates, and organoselenium compounds. The potential of such agents for cancer prevention deserves attention. Moreover, consideration needs to be given to combined modification of both nutritional and functional components of the diet, and to the adoption of new dietary patterns, starting in childhood, and based on detailed research in the field of nutrition and health and an understanding of the underlying mechanisms.

CONCLUSIONS

Genetic predisposition is clearly important in the etiology of cancer in some individuals, notably with breast and colon cancer, for which inherited mutations in cancer suppressor genes have been identified. Nevertheless, genetic predisposition as a major determinant is calculated to account for only 2–3%, at most, of the current cancer burden (Table 1). Individuals in any population have varying susceptibilities to cancer, but nutrition and food-borne components clearly affect cancer risk in the majority of populations of the world. Practical approaches to reducing cancer risk through dietary modification are available, including the Fiber First Diet,© described herein, which is compatible with other recommendations. Improved nutrition will also serve to reduce risk of other important chronic diseases. Research will help to further define the optimal diet and lifestyle, both in terms of nutritional and functional components throughout the life span, to best promote and maintain good health.

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REFERENCES

Adamson, R. H., Gustafsson, J. A., Ito, N., Nagao, M., Sugimura, T., Wakabayashi, K., and Yamazoe, Y. (Eds.) (1995). Heterocyclic amines in cooked foods: Possible human carcinogens. *Proceedings of the 23rd International Symposium Princess Takamatsu Cancer Research Fund.* Princeton Scientific Publishing, Princeton, NJ.

Adlercreutz, H., Bannwart, C., W≅h≅l≅, K., M≅kel≅, T., Brunow G., Hase, T., Arosemena, P. J., Kellis, J. T., Jr., and Vickery, L. E. (1993). Inhibition of human aromatase by mammalian lignans and isoflavonoid phytoestrogens. *J. Steroid Biochem. Molec. Biol.* **44**, 147–153.

The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group (1994). The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N. Engl. J. Med.* **334**, 1029–1035.

Aruoma, O. I. (1994). Nutrition and health aspects of free radicals and antioxidants. *Food Chem. Toxicol.* **7**, 671–683.

Barnes, S. (1997). The chemopreventive properties of soy isoflavonoids in animal models of breast cancer. *Breast Cancer Res. Treat.* **46**, 169–179.

Birt, D. F., Julius, A. D., White, L. T., and Pour, P. M. (1989). Enhancement of pancreatic carcinogenesis in hamsters fed a high-fat diet *ad libitum* and at a controlled calorie intake. *Cancer Res.* **49**, 5848–5851.

Block, G., Patterson, B., and Subar, A. (1992). Fruit, vegetables, and cancer prevention: A review of the epidemiological evidence. *Nutr. Cancer* **18**, 1–29.

Blot, W. J., Chow, W.-H., and McLaughlin, J. K. (1996). Tea and cancer: A review of the epidemiological evidence. *Eur. J. Cancer Prev.* **5**, 425–438.

Boeing, H. (1991). Epidemiological research in stomach cancer: Progress over the past ten years. *J. Cancer Res. Clin. Oncol.* **117**, 133–143.

Boone, C. W., Bacus, J. W., Bacus, J. V., Steele, V. E., and Kelloff, G. J. (1997). Properties of intraepithelial neoplasia relevant to cancer chemoprevention and to the development of surrogate endpoints for clinical trials. *Proc. Soc. Exper. Biol. Med.* **216**, 151–165.

Boyd, N. F., Martin, L. J., Noffel, M., Lockwood, G. A., and Tritchler, D. L. (1993). A meta-analysis of studies of dietary fat and breast cancer risk. *Br. J. Cancer* **68**, 627–636.

Bradlow, H. L., Fishman, J., and Osborne, M. P. (Eds.). (1997). Cancer, genetics and the environment. *Ann. N Y Acad. Sci.* **833**,

Burley, V. J. (1997). Sugar consumption and cancers of the digestive tract. *Eur. J. Cancer Prev.* **6**, 422–434.

Burley, V. J. (1998). Sugar consumption and human cancer in sites other than the digestive tract. *Eur. J. Cancer Prev.* **7**, 253–277.

Bushman, J. L. (1998). Green tea and cancer in humans: A review of the literature. *Nutr. Cancer* **31**, 151–159.

Byers, T., and Guerrero, N. (1995). Epidemiologic evidence for vitamin C and vitamin E in cancer prevention. *Am J. Clin. Nutr.* **62**, 1385–1392S.

Carroll, K. K. (1992). Dietary fat and breast cancer. *Lipids* **27**, 793–797.

Cave, W. T., Jr. (1996). Fish oil and cancer prevention. In *Nutrition and Cancer Prevention* (R. R. Watson and S. I. Mutfi, Eds.), pp. 81–90. CRC Press, Boca Raton, FL.

Caygill, C. P. J., Charlett, A., and Hill, M. J. (1998). Relationship between the intake of high-fibre foods and energy and the risk of cancer of the large bowel and breast. *Eur. J Cancer Prev.* **7**, S11–17.

Chen, W., Weisburger, J. H., Fiala, E. S., Spratt, T. E., Carmella, S. G., Chen, D. and Hecht, S. S. (1996). Gastric carcinogenesis: 2-Chloro-4-methylthiobutanoic acid, a novel mutagen in salted, pickled Sanma Hiraki fish, or similarly treated methionine. *Chem. Res. Toxicol.* **9**, 58–66.

Chyou, P. H., Nomura, A. M. Y., Hankin, J. H., and Stemmerman, G. N. (1990). A case-cohort study of diet and stomach cancer. *Cancer Res.* **50**, 7501–7504.

Clifford, C., and Kramer, B. (1993). Diet as risk and therapy for cancer. *Med. Clin. North Am.*. **77**, 725–744.

Colditz, G. A., Stampfer, M. J., and Willett, W.C. (1987). Diet and lung cancer: A review of the epidemiologic evidence in humans. *Arch. Intern. Med.* **147**, 157–160.

Correa, P. (1992). Human gastric carcinogenesis: A multistep and multifactorial process. First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res.* **52**, 6735–6740.

Correa, P., and Chen, V. W. (1994). Gastric cancer. *Cancer Surv.* **19/20**, 55–76.

Craddock, V. M. (1992). Aetiology of oesophageal cancer: Some operative factors. *Eur. J. Cancer Prev.* **1**, 89–103.

De Koster, E., Buset, M., Fernandes, E., and Deltenre, M. (1994). *Helicobacter pylori*: The link with gastric cancer. *Eur. J. Cancer Prev.* **3**, 247–257.

Dorant, E., van den Brandt, P., and Goldbohm, R. A. (1994). A prospective cohort study on *Allium* vegetable consumption, garlic supplement use, and the risk of lung carcinoma in the Netherlands. *Cancer Res.* **54**, 6148–6153.

Dwyer, J. (1993). Diet and nutritional strategies for cancer risk reduction. *Cancer* **72**(suppl. 3), 1024–1031.

Eastwood, M. A. (1992). The physiological effect of dietary fiber: An update. *Annu. Rev. Nutr.* **12**, 19–35.

Eichholzer, M., and Gutzwiller, F. (1998). Dietary nitrates, nitrates, and N-nitroso compounds, and cancer risk: A review of the epidemiologic evidence. *Nutr. Rev.* **56**, 95–105.

Farnsworth, N. R., Bingel, A. S., Cordell, G. A., Crane, F. A., and Fong, H. S. (1975). Potential value of plants as sources of new antifertility agents II. *J. Pharm. Sci.* **64**, 717–754.

Felton, J. S., and Gentile, J. M. (1997). Mutagenic/carcinogenic N-substituted aryl compounds. *Mutat. Res.* **376**, 1–276.

Fournier, D. B., Erdman, J. W., Jr., and Gordon, G. B. (1998). Soy, its components, and cancer prevention: A review of the in vitro animal and human data. *Cancer Epidemiol. Biomarkers Prev.* **7**, 1055–1065.

Franceschi, S., Boyle, P., Maisonneuve, P., La Vecchia, C., Burt, A. D., Kerr, D. J., and MacFarlane, G. J. (1993). The epidemiology of thyroid carcinoma. *Crit. Rev. Oncog.* **4**, 25–52.

Freedman, L. S., Clifford, C., and Messina, M. (1990). Analysis of dietary fat, calories, body weight, and the development of mammary tumors in rats and mice: A review. *Cancer Res.* **50**, 5710–5719.

Freudenheim, J. L., Graham, S., Horvath, P. J., Marshall, J. R., Haughey, B. P., and Wilkinson, G. (1990). Risk associated with source of fiber and fiber components in cancer of the colon and rectum. *Cancer Res.* **50**, 3295–3300.

Freudenheim, J. L., Marshall, J. R., Graham, S., Laughlin, R. Vena, J. E., Swanson, M., Ambrosone, C., and Nemoto, T. (1995). Lifetime alcohol consumption and risk of breast cancer. *Nutr. Cancer* **23**, 1–11.

Friedenreich, C. M., and Rohan, T. E. (1995). A review of physical activity and breast cancer. *Epidemiology* **6**, 311–317.

Fuchs, C. S., Giovannucci, E. L., Colditz, G. A., Hunter, D. J., Stampfer, M. J., Rosner, B., Speizer, F. E., and Willett, W. C. (1999). Dietary fiber and the risk of colorectal cancer and adenoma in women. *N. Engl. J. Med.* **340**, 169–176.

Furihata, C., Oka, M., Amin, S., Krzeminiski, J., Weisburger, J. H., Kobayashi, K., and Tatematsu, M. (1996). Effect of 2-chloro-4-methylthiobutanoic acid in a rapid bioassay for gastric carcinogens. *Cancer Lett.* **108**, 129–135.

Gallaher, D. D., Stallings, W. H., Blessing, L. L., Busta, F. F., and Brady, L. J. (1996). Probiotics, cecal microflora, and aberrant crypts in the rat colon. *J. Nutr.* **126**, 1362–1371.

Gann, P. H., Ma, J., Giovannucci, E., Willet, T., Sacks, F. M., Hennekens, C. H., and Stampfer, M. J. (1999). Lower prostate cancer risk in men with elevated plasma lycopene levels: Results of a prospective analysis. *Cancer Res.* **59**, 1225–1230.

Garewal, H. (1995). Antioxidants in oral cancer prevention. *Am J. Clin. Nutr.* **62**:1410–1416S.

Garland, C., Shekelle, R. B., Barrett-Connor, E., Criqui, M. H., Rossof, A. H., and Ogelsby, P. (1985). Dietary vitamin D and calcium and risk of colorectal cancer: A 19-year prospective study in men. *Lancet* **1**, 307–309.

Gibson, G. R., and Roberfroid, M. B. (1995). Dietary modulation of the human colon microbiota: Introducing the concept of prebiotics. *J. Nutr.* **125**, 1401–1412.

Giovannucci, E. (1999). Tomatoes, tomato-based products, lycopene, and cancer: Review of the epidemiologic literature. *J. Natl. Cancer Inst.* **91** 317–331.

Godley, P. A., Campbell, M. K., Gallagher, P., Martinson, F. E. A., Mohler, J. L., and Sandler, R. S. (1996). Biomarkers of essential fatty acid consumption and risk of prostatic carcinoma. *Cancer Epidemiol., Biomarkers. Prev.* **5**, 889–895.

Gold, E. B., and Goldin, S. B. (1998). Epidemiology of and risk factors for pancreatic cancer. *Surg. Oncol. Clin. North Am.* **7**, 67–91.

Greenberg, E. R., Baron, J. A., Tosteson, T. D., Freeman, D. H., Beck, G. J., Bond, J. H., Colacchio, T. S., Coller, J. A., Frankl, H. D., Haile, R. W., Mandel, J. S., Nierenberg, D. W., Rothestein, R., Snover, D. C., Stevens, M. M., Summers, R. W., and Stolk, R. U. (1994). A clinical trial of antioxidant vitamins to prevent colorectal adenoma. *N. Engl. J. Med.* **331**, 141–147.

Greenwald, P., Kelloff, G., Burch-Whitman, C., and Kramer, B. S. (1995). Chemoprevention. *CA Cancer J. Clin.* **45**, 31–49.

Grundy, S. M. (1996). Dietary fat. In *Present Knowledge in Nutrition* (E. E. Ziegler and L. J. Filer, Jr., Eds.), 7th ed., pp.44–57. ILSI Press, Washington, DC.

Gugler, R., Leschik, M., and Dengler, H. J. (1975). Disposition of quercetin in man after single oral and intravenous doses. *Eur. J. Clin. Pharmacol.* **9**, 229–234.

Hansson, L.-E., Nyrθn, O., Bergstr&primem, R., Wolk, A., Lindgren, A., Baron, J., and Adami, H.-O. (1994). Nutrients and gastric cancer risk: A population-based case-control study in Sweden. *Int. J. Cancer* **57**, 638–644.

Hayes, R. B., Ziegler, R. G., Gridley, G., Swanson, C., Greenberg, R. S., Swanson, G. M., Schoenberg, J. B., Silverman, D. T., Brown, L. M., Pottern, L. M., Liff, J., Schwartz, A. G., Fraumeni, J. F., Jr., and Hoover, R. N. (1999). Dietary factors and risk for prostate cancer among blacks and whites in the United States. *Cancer Epidemiol. Biomarkers Prev.* **8**, 25–34.

Hill, M. J. Cereals, cereal fiber, and colorectal cancer risk: A review of the epidemiological literature. (1998). *Eur.J. Cancer Prev.* **7**, S5–10.

Hoffman, E. L. (1937). *Cancer and Diet.* Williams and Wilkins, Baltimore, MD.

Holmberg, L., Baron, J.A., Byers, T., Wolk, A., Ohlander, E-M., Zack, M. And Adami, H-O. (1995). Alcohol intake and breast cancer risk: Effect of exposure from 15 years of age. *Cancer Epidemiol. Biomarkers Prev.* **4**, 843–847.

Howe, G. R. (1994). Dietary fat and breast cancer risks: An epidemiologic perspective. *Cancer* **74**(suppl.), 1078–1084.

Howe, G. R., and Burch, J. D. (1996). Nutrition and pancreatic cancer. *Cancer Causes Control* **7**, 69–82.

Howe, G. R. Hirohata, T., Hislop, T. G., Iscovich, J. M., Yuan, J.-M., Katsouyanni, K., Lubin, F., Marubini, E., Modan, B., Rohan, T., *et al.* (1990). Dietary factors and risk of breast cancer: Combined analysis of 12 case-control studies. *J. Natl. Cancer Inst.* **82**, 561–569.

Howe, G. R., Benito, E., Castelleto, R., Cornθe, J., EstΠve, J., Gallagher, R. P., Iscovich, J. M., Deng-ao, J., Kaaks, R., Kune, G.A., Kune, S., L=Abbθ, K. A., Lee, H. P., Lee, M., Miller, A. B., Peters, R. K., Potter, J. D., Riboli, E., Slattery, M. L., Trichopoulos, D., Tuyns, A., Tzonou, A., Whittemore, A. S., Wu-Williams, A. H., and Shu, Z. (1992). Dietary intake of fiber and decreased risk of cancers of the colon and rectum: Evidence from the combined analysis of 13 case-control studies. *J. Natl. Cancer Inst.* **84**, 1887–1896.

Howson, C. P., Hiyama, T., and Wynder, E. L. (1986). The decline in gastric cancer: Epidemiology of an unplanned triumph. *Epidemiol. Rev.* **8**, 1–27.

Hwang, H., Dwyer, J., and Russell, R. M. (1994). Diet, helicobacter pylori infection, food preservation, and gastric cancer risk: Are there new roles for preventative factors? *Nutr. Rev.* **52**, 75–83.

International Agency for Research on Cancer (1987). IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans: *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs,* Vols. 1–42, pp. 83–85, Suppl. 7. IARC, Lyon, France.

International Agency for Research on Cancer (1988). IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans: Alcohol Drinking, Vol. 44. IARC, Lyon, France.

International Agency for Research on Cancer (1991). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Coffee, Tea, Mate, Merthylxanthines and Methylglyoxal. Vol. 51, pp. 41–206. IARC, Lyon, France.

Jacobs, D. R., Jr., Marquart, L., Slavin, J., and Kushi, L. H. (1998). Whole-grain intake and cancer: An expanded review and meta-analysis. *Nutr. Cancer* **30**, 85–96.

Jones, G. M. (1992). Food additives. In *Food Safety*, pp. 239. Eagan Press, St. Paul, MN.

Johnson, I. T. (1998). Antioxidants and anticarcinogens. *Eur. J. Cancer Prev.* **7**(suppl. 2), S55–62.

Kampman, E., Slattery, M. L., Bigler, J., Leppert, M., Samowitz, W., Caan, B. J., and Potter, J. D. (1999). Meat consumption, genetic susceptibility, and colon cancer risk: A United States multicenter case-control study. *Cancer Epidemiol. Biomarkers Prev.* **8**, 15–24.

Katiyar, S., and Mukhtar, H. (1996). Tea in chemoprevention of cancer: Epidemiologic and experimental studies (Review). *Int. J. Oncol.* **8**, 221–238.

Keenan, K. P., Ballam, G. C., Dixit, R., Soper, K. A., Laroque, P., Mattson, B. A., Adams, S. P., and Coleman, J. B. (1997). The effects of diet, over-feeding, and moderate dietary restriction on Sprague-Dawley rat survival, disease, and toxicology. *J. Nutr.* **127**, 851–856S.

Klurfeld, D. M. (1992). Dietary fiber-mediated mechanisms in carcinogenesis. *Cancer Res.* **52**, 2055–2059s.

Kneller, R. W., Guo, W. D., Hsing, A. W., Chen, J. S., Blot, W. J., Li, J. Y., Forman, D., and Fraumeni, J. F., Jr. (1992). Risk factors for stomach cancer in sixty-five Chinese counties. *Cancer Epidemiol. Biomarkers Prev.* **1**, 113–118.

Krey, G., Braissant, O., L=Horset, F., Kalkhoven, E., Perroud, M., Parker, M. G., and Wahli, W. (1997). Fatty acids, eicosanoids, and hypolipidemic agents identified as ligands of peroxisome proliferator-activated receptors by coactivator-dependent receptor ligand assay. *Mol. Endocrinol.* **11**, 779–791

Kritchevsky, D. (1995). The effect of over-and undernutrition on cancer. *Eur. J. Cancer Prev.* **4**, 445–451.

Kune, G. A., and Vitetta, L. (1992). Alcohol consumption and the etiology of colorectal cancer: A review of the scientific evidence from 1957 to 1991. *Nutr. Cancer* **18**, 97–111.

Kurzer, M. S., and Xu, X. (1997). Dietary phytoestrogens. *Annu. Rev. Nutr.* **17**, 353–381.

Lachance, P., and Langseth, L. (1994). The RDA concept: Time for a change? *Nutr. Rev.* **52**, 266–270.

Landis, S. H, Murray, T., Bolden, S., and Wingo, P. A. (1998). Cancer statistics–1998. *CA Cancer J. Clin.* **48**, 26–29.

La Vecchia, C., Ferraroni, M., Franceschi, S., Mezzetti, M., Decarli, A., and Negri, E. (1997). Fibers and breast cancer risk. *Nutr. Cancer* **28**, 264–269.

Layton, D. W., Bogen, K. T.,Knize, M. G., Hatch, F. T., Johnson, V. M., and Felton, J. (1995). Cancer risk of heterocyclic amines in cooked foods: An analysis and implications for research. *Carcinogenesis* **16**, 39–52.

Le Marchand, L., Kolonel, L. N., Wilkens, L. R., Myers, B. C., and Hirohata, T. (1994). Animal fat consumption and prostate cancer: a prospective study in Hawaii. *Epidemiology* **5**, 276–282.

Le Marchand, L., Wilkens, L. R., Kolonel, L. N., Hankin, J. H., and Lyu, L-C. (1997). Associations of sedentary lifestyle, obesity, smoking, alcohol use, and diabetes with the risk of colorectal cancer. *Cancer Res.* **57**, 4787–4794.

Le Marchand, L. L., Yoshizawa, C. N., Kolonel, L. N., Hankin, J. H., and Goodman, M. T. (1989). Vegetable consumption and lung cancer risk: A population-based case-control study in Hawaii. *J. Nat. Cancer Inst.* **81**, 1158–1164.

Lipkin, M. and Newmark, H. (1995). Calcium and the prevention of colon cancer. *J. Cell. Biochem.* **22**(suppl..) 65–73.

Longnecker, M. P., Paganini-Hill, A., and Ross, R. K. (1995). Lifetime alcohol consumption and breast cancer risk among postmenopausal women in Los Angeles. *Cancer Epidemiol. Biomarkers Prev.* **4**, 721–725.

Lyon, J. L., Slattery, M. L., Mahoney, A. W., and Robison, L. M. (1993). Dietary intake as a risk factor for cancer of the exocrine pancreas. *Cancer Epidemiol. Biomarkers Prev.* **2**, 513–518.

Martinez, M. E., and Willett, W. C. (1998) Calcium, vitamin D, and colorectal cancer: A review of the epidemiologic evidence. *Cancer Epidemiol. Biomarkers Prev.* **7**, 163–168.

Martin-Moreno, J. M., Willett, W. C., Gorgojo, L., Banegas, J. R., Rodriguez-Artalejo, F., Fernandez-Rodriguez, J. C., Maisonneuve, P., and Boyle, P. (1994). Dietary fat, olive oil intake, and breast cancer risk. *Int. J. Cancer* **58**, 774–780.

Masoro, E. J. (1991). Caloric restriction and aging in rats. In *The Potential for Nutritional Modulation of Aging Processes* (D. K. Ingram, G. T. Baker, III, and N. W. Shock, Eds.), pp. 123, Food & Nutrition Press, Trumbull, CN.

McLaughlin, J. K., Gridley, G., Block, G., Winn, D. M., Preston- Martin, S., Schoenberg, J. B., and Messina, M. (1995). Modern applications for an ancient bean: Soybeans and the prevention and treatment of chronic disease. *J. Nutri.* **125**, 567–569S.

Mettlin, C. (1997). Clinical oncology update: Prostate cancer: Recent developments in the epidemiology of prostate cancer. *Eur.. J. Cancer* **33**, 340–347.

Micozzi, M. S., and Moon, T. E. (Eds.) (1992). *Nutrition and Cancer Prevention II: Investigating the Role of Macronutrients*. Marcel Dekker, New York.

Miller, A. B., Berrino, F., Hill, M., Pietinen, P., Riboli, E., and Wahrendorf, J. (1994). Diet in the aetiology of cancer: A review. *Eur. J. Cancer* **30**, 207–220.

Mirvish, S. S. (1994). Experimental evidence for inhibition of N-nitroso compound formation as a factor in the negative correlation between vitamin C consumption and the incidence of certain cancers. *Cancer Res.* **54**, 1948–1951.

National Research Council (1996). *Carcinogens and Anticarcinogens in the Human Diet.* National Academy Press, Washington, DC.

Negri, E., Franceschi, S., Parpinel, M., and La Vecchia, C. (1998). Fiber intake and risk of colorectal cancer. *Cancer Epidemiol. Biomarkers Prev.* **7**, 667–671.

Neugut, A. I., Hayek, M., and Howe, G. (1996). Epidemiology of gastric cancer. *Semin. Oncol.* **23**, 281–291.

Nomura, A. M. Y., and Kolonel, L. N. (1991). Prostate cancer: A current perspective. *Epidemiol. Rev.* **13**, 200–227.

Nomura, A. M. Y., Ziegler, R. G., Stemmermann, G. N., Chyou, P.-H., and Craft, N. E. (1997). Serum mirconutrients and upper aerodigestive tract cancer. *Cancer Epidemiol., Biomarkers, Prev.* **6**, 407–412.

Olson, J. A. (1996). Benefits and liabilities of vitamin A and carotenoids. *J. Nutr.* **126**, 1208–1212S.

Omenn, G. S., Goodman, G. E., Thornquist, M. D., Balmes, J., Cullen, M. R., Glass, A., Keogh, J. P., Meyskens, F. L., Jr., Valanis, B., Williams, J. H., Jr., Barnhart, S., Cherniack, M. G., Brodkin, C. A., and Hammar, S. (1996). Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial. *J. Natl. Cancer Inst.* **88**, 1550–1559.

Pariza, M. W., and Boutwell, R. K. (1987). Historical perspective: Calories and energy expenditure in carcinogenesis. *Am. J. Clin. Nutr.* **45**(suppl. 1), 151–156.

Pool-Zobel, B. L., Bub, A., Liegibel, U. M., Treptow-van Lishaut, S., and Rechkemmer, G. (1998). Mechanisms by which vegetable consumption reduces genetic damage in humans. *Cancer Epidemiol. Biomarkers Prev.* **7**, 891–899.

Potter, J. D. (1996). Nutrition and colon cancer. *Cancer Causes Control* **7**, 127–146.

Potter, J. D., Slattery, M. L., Bostick, R. M., and Gapstur, S. M. (1993). Colon cancer: A review of the epidemiology. *Epidemiol. Rev.* **15**, 499–545.

Reddy, B. S. (1996). Dietary fat and colon cancer: Role in cancer prevention. In *Nutrition and Cancer Prevention* (R. R. Watson and S. I. Mufti, Eds.), pp. 105–118. CRC Press, Boca Raton, FL.

Reddy, B. S., Hamid, R., and Rao, C. V. (1997). Effect of dietary oligofructose and inulin on colonic preneoplastic aberrant crypt foci inhibition. *Carcinogenesis* **18**, 1371–1374.

Reinli, K., and Block, G. (1996). Phytoestrogen content of foods: A compendium of literature values. *Nutr. Cancer* **26**, 123–148.

Rolls, B. J., and Hill, J. O. (1998). *Carbohydrates and Weight Management.* ILSI Press, Washington, DC.

Rose, D. P. (1990). Dietary fiber and breast cancer. *Nutr. Cancer* **13**, 1–8.

Rose, D. P., and Connolly, J. M. (1993). Effects of dietary omega-3 fatty acids on human breast cancer growth and metastases in nude mice. *J. Natl. Cancer Inst.* **85**, 1743–1747.

Rosenberg, L., Metzger, L. S., and Palmer, J. R. (1993). Alcohol consumption

and risk of breast cancer: A review of the epidemiologic evidence. *Epidemiol. Rev.* **15**, 133–144.

Sardesai, V. M. (1992). Nutritional role of polyunsaturated fatty acids. *J. Nutr. Biochem.* **3**, 154–165.

Schottenfeld, D. (1995). Epidemiology of endometrial neoplasia. *J. Cell. Biochem.* **23**(suppl.), 151–159.

Seitz, H. K., Simanowski, U. A., Garzon, F. T., Rideout, J. M., Peters, T. J., Koch, A., Berger, M. R., Einecke, H., and Maiwald, M. (1990). Possible role of acetaldehyde in ethanol-related rectal cocarcinogenesis in the rat. *Gastroenterology* **98**, 406–413.

Shils, M. D., Olson, J. A., and Shike, M. (Eds.) (1994). *Modern Nutrition in Health and Disease*, 8th ed. Lea & Febiger, Philadelphia.

Singh, J., Hamid, R., and Reddy, B. S. (1997). Dietary fat and colon cancer: Modulation of cyclooxygenase-2 by types and amount of dietary fat during the post-initiation stage of colon carcinogenesis. *Cancer Res.* **57**, 3465–3470.

Sinha R., Chow, W. H., Kulldorf, M., Denobile, J., Butler, J., Garcia-Closas, M., Weil, R., Hoover, R. N., and Rothman, N. (1999). Well-done, grilled red meat increases the risk of colorectal adenomas. *Cancer Res.* **59**, 4320–4324.

Sokol, R. J. (1996). Vitamin E. In *Present Knowledge in Nutrition*, 7th ed. (E. E. Ziegler and L. J. Filer, Jr., Eds.), pp. 130–136. ILSI Press, Washington, DC.

Soler, M., Chatenoud, L., La Vecchia, C., Franceschi, S., and Negri, E. (1998). Diet, alcohol, coffee, and pancreatic cancer: Final results from an Italian study. *Eur. J Cancer Prev.* **7**, 455–460.

Steinmetz, K., and Potter, J. D. (1991). Vegetables, fruit, and cancer: I. Epidemiology. *Cancer Causes Control* **2**, 325–357.

Sugimura, T. (1996). An overview of cancer prevention. *Eur. J. Cancer Prev.* **5**(suppl. 2), 1–8.

Swanson, C. A., Brown, C. C., Brownson, R. C., Alavanja, M. C. (1997). Re: Saturated fat intake and lung cancer among nonsmoking women in Missouri. *J. Natl. Cancer Inst.* **89**, 1724–1725.

Takahashi, M., Kokubo, T., Furukawa, F., Kurokawa, Y., Tatematsu, M., and Hayashi, Y. (1983). Effect of high salt diet on rat gastric carcinogenesis induced by N-methyl-N′-nitro-N-nitrosoguanidine. *Gann* **74**, 28–34.

Takezaki, T., Hirose, K., Inoue, M., Hamajima, N., Kuroishi, T., Nakamura, S., Koshikawa, T., Matsuura, H., and Tajima, K. (1996). Tobacco, alcohol, and dietary factors associated with the risk of oral cancer among Japanese. *Jpn. J. Cancer Res.* **87**, 555–562.

Tannenbaum, A. (1942). The genesis and growth of tumors. II Effects of caloric restriction per se. Cancer Res. 1942;2:460–7.

Tannenbaum, A. (1959). Nutrition and cancer. In *Physiopathology of Cancer* (F. Homburger, Ed.), pp. 517–562. Phiebig, White Plains, NY.

Toma, S., Losardo, P. L., Vincent, M., and Palumbo, R. (1995). Effectiveness of β-carotene in cancer chemoprevention. *Eur. J. Cancer Prev.* **4**, 213–224.

Tominaga, S., and Kuroishi, T. (1997). An ecological study on diet/nutrition and cancer in Japan. *Int. J. Cancer* **10**(suppl.), 2–6.

Trichopoulos, D., Ouranos, D., Day, N. E., Tzonou, A., Manusos, O., Papadimitriou, C., and Trichopoulos, A. (1985). Diet and cancer of the stomach: A case-control study in Greece. *Int. J. Cancer* **36**, 291–297.

Trichopoulou, A., Katsouyanni, K., Stuver, S., Tzala, L., Gnardellis, C., Rimm, E., and Trichopoulos, D. (1995). Consumption of olive oil and specific food groups in relation to breast cancer risk in Greece. *J. Nat. Cancer Inst.* **87**, 110–116.

Trowell, H. (1974). Definitions of fibre. *Lancet* **1**, 503.

Vainio, H., and Rautalahti, M. (1998). An international evaluation of the cancer preventive potential of carotenoids. *Cancer Epidemiol. Biomarkers Prev.* **7**, 725–728.

Vainio, H., and Rautalahti, M. (1999). An international evaluation of the cancer preventive potential of vitamin A. *Cancer Epidemiol., Biomarkers, Prev.* **8**, 107–109.

van Poppel, G. and Goldbohm, R. A. (1995). Epidemiologic evidence for &exists;-carotene and cancer prevention. *Am. J. Clin. Nutr.* **62**, 1393–1402S.

Wattenberg, L. W. (1992). Inhibition of carcinogenesis by minor dietary constituents. *Cancer Res.* **52**(suppl.), 2085–2091s.

Weber, P., Bendich, A., and Schalch, W. (1996). Vitamin C and human health: A review of recent data relevant to human requirements. *Int. J. Vitam. Nutr. Res.* **66**, 19–30.

Weisburger, J. H. (1997a). Dietary fat and risk of chronic disease: Mechanistic insights from experimental studies. *J. Am. Diet Assoc.* **97**(suppl.), S16–22.

Weisburger, J. H. (1997b). Tea and health: A historical perspective. *Cancer Lett.* **114**, 315–317.

Weisburger, J. H. (1998a). Chemoprevention of cancer by tea. In *Cancer and Nutrition* (K. N. Prasad and W.C. Cole, Eds.), pp. 167–171. IOS Press, Amsterdam.

Weisburger, J. H. (1998b). Can cancer risks be altered by changing nutritional traditions? *Cancer* **83**, 1278–1281.

Weisburger, J. H. (Ed.) (1998c). International symposium on lycopene and tomato products in disease prevention: An introduction. *Proc. Soc. Exp. Biol. Med.* **218**, 93–94.

Weisburger, J. H., Dolan, L., Pittman, B. (1998) Inhibition of PhIP mutagenicity by caffeine, lycopene, daidzein, and genistein. *Mutat. Res.* **416**, 125–128.

Weisburger, J. H., and Williams, G. M. (1995). Causes of cancer. In *American Cancer Society Textbook of Clinical Oncology* (G. P. Murphy, W. Lawrence, Jr., and R. E. Lenhard, Jr., Eds.), pp. 10–39. American Cancer Society, Atlanta, GA.

Welsch, C. W. (1992). Relationship between dietary fat and experimental mammary tumorigenesis: A review and critique. *Cancer Res.* **52**(suppl. 7), 2040–2048s.

White, E., Shannon, J. S., and Patterson, R. E. (1997). Relationship between vitamin and calcium supplement use and colon cancer. *Cancer Epidemiol. Biomarkers and Prev.* **6**, 769–774.

Whitney, E. N., and Hamilton, E. M. N. (1981). *Understanding Nutrition*, 2nd ed. West Publishing, St. Paul, MN.

Whysner, J., and Williams, G. M. (1996). Saccharin mechanistic data and risk assessment: Urine composition, enhanced cell proliferation, and tumor promotion. *Pharmacol. Ther.* **71**, 225–251.

Willett, W. C. (1994). Diet and health: What should we eat? *Science* **264**, 532–537.

Willett, W. C., and Hunter, D. J. (1994). Vitamin A and cancers of the breast, large bowel, and prostate: Epidemiologic evidence. *Nutr. Rev.* **52**, S53–59.

Williams, C. L. (1995a). A summary of conference recommendations on dietary fiber in childhood. *Pediatrics* **96**, 1023–1028.

Williams, C. L. (1995b). Importance of dietary fiber in childhood. *J. Am. Diet. Assoc.* **95**, 1140–1146.

Williams, C. L. (1996). Nutrition in childhood: A key component of primary cancer prevention. In *Nutrition and Cancer Prevention* (R. R.Watson and S. I. Mufti, Eds.), pp. 25–50. CRC Press, Boca Raton, FL.

Williams, C. L., and Bollella, M.(1995). Is a high fiber diet safe for children? *Pediatrics* **96**, 1014–1019.

Williams, C. L., Bollella, M., and Williams, G. M. (1993). Cancer prevention beginning in childhood. In *Cancer Prevention* (V. T. DeVita, Jr., S. Hollman, and S. A. Rosenberg, Eds.), pp. 1–13. J. B. Lippincott Co., Philadelphia, PA.

Williams, C. L., Bollella, M., and Wynder, E. (1995). A new recommendation for dietary fiber in childhood. *Pediatrics* **96**, 985–988.

Williams, G. M. (1993a). Food: its role in the etiology of cancer. In *Food and Cancer Prevention: Chemical and Biological Aspects* (K. W. Waldron, I. T. Johnsen, and G. R. Genwick, Eds.), pp. 3–11. The Royal Society of Chemistry, Cambridge, U.K.

Williams, G. M. (1993b). Inhibition of chemical-induced experimental cancer by synthetic phenolic antioxidants. In *Antioxidants: Chemical Physicological, Nutritional and Toxicological Aspects* (G. M. Williams, H. Sies, G. T. Baker III, C. J. H. Erdman, Jr., Eds.), pp. 303–308. Princeton Scientific Press, Princeton, NJ.

Williams, G. M. (1994). Interventive prophylaxis of liver cancer. *Eur. J. Cancer Prev.* **3**, 89–99.

Williams, G. M., and Weisburger, J. H. (1991). Chemical carcinogenesis. In *Casarett and Doull's Toxicology: The Basic Sciences of Poisons*, 4th ed. (M. O. Amdur, J. Doull, and C. D. Klaassen, Eds.), pp. 127–200. Pergamon Press, New York.

Williams, G. M., and Wynder, E. L. (1996). Diet and cancer: A synopsis of causes and prevention strategies. In *Nutrition and Cancer Prevention* (R. R. Watson, and S. I. Mufti, Eds.), pp. 1–12. CRC Press, Boca Raton, FL.

Williams, W. R. (1908). *The Natural History of Cancer.* William Wood, New York.

Williamson, G., Faulkner, K., and Plumb, G. W. (1998). Glucosinolates and phenolics as antioxidants from plants foods. *Eur. J. Cancer Prev.* **7**, 17–21.

Wolk, A., Gridley, G., Niwa, S., Lindblad, P., McCredie, M., Mellemgaard, A., Mandel, J. S., Wahrendorf, J., McLaughlin, J. K., and Adami, H.-O. (1996). International renal cell cancer study: VII. Role of diet. *Int. J. Cancer* **65**, 67–73.

World Cancer Research Fund (1997). *Food, Nutrition and the Prevention of Cancer: A Global Perspective.* American Institute for Cancer Research, Washington, DC.

Wu, A., Pike, P. C., and Stram, D. O. (1999). Meta-analysis: Dietary fat intake, serum estrogen levels, and the risk of breast cancer. *J. Natl. Cancer Inst.*, **91**, 524–534.

Wynder, E. L., Weisburger, J. H., and Ng, S. K. (1992). Nutrition: The need to define "optimal" intake as a basis for public policy decisions. *Am. J. Public Health* **82**, 346–350.

Wynder, E. L., and Williams, G. M. (1993). Metabolic overload and carcinogenesis from the viewpoint of epidemiology. In *Chemical Carcinogenesis: The Relevance of Mechanistic Understanding in Toxicological Evaluations* (A. Somogyi, K. E. Appel, and A. Katenkamp, Eds.), pp. 17–24. MMV Medizin Verlag GmbH, Mηnchen.

Yang, C. S., and Wang, Z.-Y. (1993). Tea and cancer. *J. Natl. Cancer Inst.* **85**, 1038–1049.

Zhang, S., Hunter, D. J., Forman, M. R., Rosner, B. A., Speizer, F. E., Colditz, G. A., Manson, J. E., Hankinson, S. E., and Willett, W. C. (1999). Dietary Carotenoids and Vitamins A, C, and E and risk of breast cancer. *J. Natl. Cancer Inst.* **91**, 547–556.

Zumbé, A. (1998). Polyphenols in cocoa: are there health benefits? *BNF Nutr. Bull.* **23**, 94–102

EXHIBIT 3

Before the
FOOD AND DRUG ADMINISTRATION
Rockville, MD

In re: Guidance for Industry: Significant Scientific Agreement In the Review of Health Claims For Conventional Foods and Dietary Supplements; Availability	)))))	Docket No. 99D-5424

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COMMENTS OF JULIAN M. WHITAKER, M.D.; PURE ENCAPSULATIONS, INC.; XCEL MEDICAL PHARMACY, LTD.; MYCOLOGY RESEARCH LABORATORIES, LTD.; DURK PEARSON and SANDY SHAW; and AMERICAN PREVENTIVE MEDICAL ASSOCIATION

Julian M. Whitaker, M.D.; Pure Encapsulations, Inc.; XCEL Medical Pharmacy, Ltd.; Mycology Research Laboratories, Ltd.; Durk Pearson and Sandy Shaw; and the American Preventive Medical Association (collectively, "Joint Commenters"), hereby submit their comments in response to the agency's solicitation for comments in the above-referenced docket. See 64 Fed. Reg. 71794 (1999).

BACKGROUND OF JOINT COMMENTERS

Julian M. Whitaker, M.D. Julian M. Whitaker, M.D. ("Dr. Whitaker) is a physician licensed to practice medicine in the states of California and Washington. He graduated from Dartmouth College in 1966 with a B.S. degree and from Emory University in 1970 with an M.D. degree. He received additional training in surgery as a resident at the University of California Medical School. From 1975 to 1976 he worked as a physician at the Pritikin Institute in California. Since that time he has been the clinical director of the Whitaker Wellness Institute in Newport Beach, California. He is the author of five books: ***Reversing Heart Disease*** (1985), ***Reversing Diabetes*** (1987),

Reversing Health Risk (1989), ***Natural Healing*** (1994), and ***What Your Doctor Won't Tell You About Bypass*** (1995). Since August of 1991 he has been the editor of ***Health & Healing***, currently the nation's largest single editor health newsletter. In 1996, ***Health & Healing*** had over 500,000 subscribers. He receives royalties from the distribution and sale of several dietary supplements. Dr. Whitaker has filed with FDA several health claim petitions and would like to use the health claims on the labels and in the labeling of dietary supplements. He therefore has a keen interest in how FDA interprets its health claim standard and is adversely affected by FDA's insistence on a standard more rigorous than that intended by Congress.

Durk Pearson and Sandy Shaw. Durk Pearson and Sandy Shaw ("Pearson and Shaw") are scientists residing in Nevada. They design dietary supplement formulations and license them to manufacturing and retailing companies. They are authors of four books on aging and age-related diseases, including the #1, million plus copy best seller ***Life Extension: A Practical Scientific Approach*** (1982). They have also published three other health books, two of which were best sellers: ***The Life Extension Companion*** (1984); ***The Life Extension Weight Loss Program*** (1986); and ***Freedom of Informed Choice—FDA Versus Nutrient Supplements*** (1993). Durk Pearson and Sandy Shaw were plaintiffs in the *Pearson v. Shalala* case that is the subject of these comments. Pearson and Shaw license dietary supplements. They have filed with FDA several health claim petitions and would like to use the health claims on the labels and in the labeling of dietary supplements. They therefore have a keen interest in how FDA interprets its health claim standard and are adversely affected by FDA's insistence on a standard more rigorous than that intended by Congress.

American Preventive Medical Association. The American Preventive Medical Association ("APMA") is a non-profit organization in Virginia. APMA was founded in October of 1992 and is dedicated to ensuring consumer access to preventive therapies and the rights of health care providers to offer those therapies. APMA was a plaintiff in the *Pearson v. Shalala* case that sought FDA approval of four health claims. Several APMA practitioner members sell dietary supplements and would like to use the health claims on the labels and in the labeling of those supplements. APMA practitioner members are desirous of filing additional health claim petitions with FDA. In addition, APMA and its practitioner members and their hundreds of thousands of patients would benefit from an effective and meaningful health claim approval process as described herein because it would enable them to communicate and receive nonmisleading health information on labels and in labeling of dietary supplements. APMA and its members therefore have a keen interest in how FDA interprets its health claim standard and are adversely affected by FDA's insistence on a standard more rigorous than that intended by Congress.

Mycology Research Labs Ltd. Mycology Research Labs Ltd. ("Mycology") is a corporation organized in Great Britain and engaged in the business of manufacturing, distributing, and selling multiple pharmaceutical grade dietary supplements for human consumption around the world, including in the United States. Mycology is desirous of filing with FDA several health claim petitions and would like to use the health claims on the labels and in the labeling of dietary supplements that it manufactures, distributes, and sells in the United States. It therefore has a keen interest in how FDA interprets its health claim standard and is adversely affected by FDA's insistence on a standard more rigorous than that intended by Congress.

Pure Encapsulations, Inc. Pure Encapsulations, Inc. ("Pure") is a Massachusetts corporation engaged in the business of manufacturing, distributing, and selling pharmaceutical grade dietary supplements for human and companion animal consumption. Pure has filed with FDA several health claim petitions and would like to use the health claims on the labels and in the labeling of dietary supplements. It therefore has a keen interest in how FDA interprets its health claim standard and is adversely affected by FDA's insistence on a standard more rigorous than that intended by Congress.

XCEL Medical Pharmacy, LTD d/b/a XCEL Health Care. XCEL Medical Pharmacy, LTD d/b/a XCEL Health Care ("XCEL") is a California corporation engaged in the business of manufacturing, distributing, and selling pharmaceutical grade dietary supplements for human consumption. XCEL is desirous of filing with FDA health claim petitions and would like to use health claims on the labels and in the labeling of dietary supplements that it manufactures, distributes, and sells. It therefore has a keen interest in how FDA interprets its health claim standard and is adversely affected by FDA's insistence on a standard more rigorous than that intended by Congress.

BACKGROUND OF AGENCY NOTICE

In 21 U.S.C. § 343(r)(5(D), Congress assigned the Food and Drug Administration the task of establishing a "procedure and standard respecting the validity of [the health] claim." The FDA, however, did not provide regulatees with a defined standard for review of health claims. On January 15, 1999, the United States District Court for the District of Columbia held the FDA's failure to define a standard for dietary supplement health claims a violation of the Administrative Procedure Act (APA). *Pearson v.*

Shalala, 164 F.3d 650, 659-661 (D.C. Cir.1999), *reh'g denied en banc,* 172 F.3d 72 (D.C. Cir. 1999).

In particular, the Court held FDA's failure to give definitional content to the phrase "significant scientific agreement" (its lode stone in reviewing dietary supplement health claims) a violation of the APA's prohibition on arbitrary and capricious agency action. *Pearson*, 164 F.3d at 660-661. The Court reasoned that "[i]t simply will not do for a government agency to declare—without explanation—that a proposed course of private action is not approved." It further reasoned that "[t]o refuse to define the criteria [the agency] is applying is equivalent to simply saying no without explanation." *Id.*

The Court held that FDA was required either case by case or sub-regulation by sub-regulation to define the standard, to "explain what [FDA] means by significant scientific agreement or, at minimum, what it does not mean." *Pearson*, 164 F.3d at 661. The Court required FDA to define the standard in a manner that would make it "possible for the regulated class to perceive the principles which are guiding agency action." *Id.*.

The Court explained that it could be possible for FDA to define a standard with sufficient particularity that would satisfy the Administrative Procedure Act but yet not define it with that degree of particularity required to satisfy the First or Fifth Amendments to the United States Constitution. *Pearson,* 164 F.3d at 660 n.12.

On December 22, 1999, the FDA responded to the APA holding in the *Pearson* Court's remand not by promulgating a new rule but by issuing a notice of a guidance. 64 Fed. Reg. 71794 (Dec. 22, 1999). In its Guidance, FDA explains that it reviews "all relevant studies" concerning the nutrient/disease relationship and does so under a hierarchy that deems interventional studies involving randomized, controlled clinical

trials as the "gold standard." Guidance at 4-5. Next down from the randomized, controlled clinical trials are observational studies, with greater preference accorded prospective than retrospective studies. Observational studies are, themselves, given a hierarchy: (1) cohort (longitudinal) studies; (2) case-control studies; (3) cross-sectional studies; (4) uncontrolled case series or cohort studies; (5) time-series studies; (6) ecological or cross-population studies; (7) descriptive epidemiology; and (8) case reports. Below observational studies are the following in their order of relative weight and significance: (1) research synthesis studies and (2) animal and in vitro studies. Guidance at 5.

The agency next discusses its method for ascertaining whether the studies include reliable measures of the substance and the disease or health-related condition. Guidance at 7. FDA states that it must identify "biomarkers (immediate or surrogate endpoint markers) for the presence or risk of disease." Guidance at 7. FDA states that it must be able to identify and measure the substance in a food and determine the impact of that measured substance on the disease or health-related condition exclusive of other dietary components or the food itself. Guidance at 8-9.

In evaluating scientific studies, FDA will assess the susceptibility of the study to bias and confounders; quality assessment criteria (including adequacy and clarity of design; population studied; analytical methodology and quality control procedures); and the statistical methods used. Guidance at 10-13.

In evaluating the totality of the scientific evidence, FDA requires proof that "a change in the dietary intake of the substance ***will*** result in a change in a disease endpoint." Guidance at 13 (emphasis added). Moreover, it requires proof of causation,

demanding strong evidence of a causal relationship. Guidance at 14-15. The agency depends primarily on use of interventional studies (randomized, controlled clinical trials) as a condition precedent to proof of causation, writing:

> Causality can be best established by interventional data, particularly from randomized, controlled clinical trials, that show that altering the intake of an appropriately identified and measured substance results in a change in a valid measure of a disease or health-related condition. In the absence of such data, a causal relationship may be inferred based on observational and mechanistic data through strength of association, consistency of association, independence of association, dose-response relationship, temporal relationship, effect of dechallenge, specificity, and explanation of a pathogenic mechanism or a protective effect against such a mechanism (biological plausibility). Although these features strengthen the claim that a substance contributes to a certain health outcome, they do not prove that eating more or less of the substance will produce a clinically meaningful outcome. In many cases (for example, if the intake of the substance has not been or cannot be assessed adequately in available observational studies because it has not been commonly consumed or its intake cannot be assessed independently of other substances), controlled clinical trials are necessary to establish the validity of a substance/disease relationship.

Guidance at 15.

In determining the weight of the scientific evidence, FDA requires that two questions be answered in the affirmative: (1) whether the evidence in support of the substance/disease relationship outweighs that against it and (2) whether the evidence corroborates "that a change in the dietary intake of the substance ***will*** result in a change in the disease endpoint." Guidance at 16 (emphasis added).

In the all-important matter of defining "significant scientific agreement," FDA states that "[i]n the process of scientific discovery, significant scientific agreement occurs well after the state of emerging science, where data and information permit an inference, but before the point of unanimous agreement within the relevant scientific community that the inference is valid." Guidance at 16. The agency states that "significant scientific agreement is not consensus in the sense of unanimity, it represents considerably more

than an initial body of emerging evidence." Guidance at 16-17. In assessing whether significant scientific agreement exists, FDA states that it will "take[] into account the viewpoints of qualified experts outside the agency. . ." Guidance at 18. It states that it will "take into account:

> • *review publications that critically summarize data and information in the secondary scientific literature;*
> • *documentation of the opinion of an "expert panel" that is specifically convened for this purpose by a credible, independent body;*
> • *the opinion or recommendation of a federal government scientific body such as the National Institutes of Health (NIH) or the Centers for Disease Control and Prevention (CDC); or the National Academcy of Sciences (NAS); or an independent, expert body such as the Committee on Nutrition of the American Academy of Pediatrics (AAP), the American Heart Association (AHA), American Cancer Society (ACS), or task forces or other groups assembled by the National Institutes of Health (NIH).*

Guidance at 18.

SUMMARY

The United States Court of Appeals' mandate to FDA is to "explain what [FDA} means by significant scientific agreement or, at minimum, what [FDA] does not mean." *Pearson*, 164 F.3d at 661. The Guidance fails to comply with the mandate. While in the Guidance FDA has listed the rank it accords to varying types of scientific evidence (without specifying the comparative or cumulative weight of the different kinds of evidence) and has indicated that it expects near conclusive proof of causality as a condition precedent to claim approval, it has avoided explaining what it means by significant scientific agreement; it has also avoided explaining what it does not mean.

The Court's mandate asks FDA to provide the regulated class sufficient information "to perceive the principles which are guiding agency action." The Guidance does not provide information necessary for regulatees to perceive FDA's guiding

principles. It does not explain the meaning of significant scientific agreement. While, from the Guidance, the regulated class can understand that FDA views interventional studies involving well designed randomized, controlled clinical trials as its "gold standard," it is entirely impossible from the Guidance to perceive whether FDA will ever accept studies other than interventional or other than those involving randomized, controlled clinical trials as sufficient for claim authorization. It appears unlikely that FDA ever will because it requires proof of direct causality. Given FDA's insistence on proof of direct causality (that a substance ***will*** result in a change in a disease endpoint) as a condition precedent to claim approval, it appears that only claims backed by well designed randomized, controlled clinical trials coupled with proof of direct causality will cause FDA to permit claim authorization. A large body of evidence strongly supporting, but not conclusively proving, a substance-disease relationship appears unlikely to satisfy the FDA.

Thus, the only principle that regulatees can perceive with clarity from FDA's Guidance is that FDA will accept the same kind of near conclusive proof expected as a condition precedent for drug approval as a condition precedent for dietary supplement claim approval. That principle violates Congressional intent, however. Congress plainly expects this agency to authorize health claims for dietary supplements without requiring that those claims be backed by the same kind of near conclusive proof required for the grant of applications for new drugs. Accordingly, to the extent that FDA's Guidance reveals a principle to the regulated class, that principle is one calling for a level of evidence that Congress has unequivocally rejected in the context of health claims for dietary supplements.

In addition, FDA's Guidance includes an unscientific bias and favoritism for certain non-governmental organizations, namely the Committee on Nutrition of the American Academy of Pediatrics, the American Heart Association, and the American Cancer Society. The agency places special emphasis upon the opinions and recommendations of these private organizations equating the value of those with the opinions and recommendations of federal government scientific bodies. It omits from specific reference the opinions and recommendations of other private bodies, such as universities, professional and scientific associations, and other scientific authorities. The action reveals an unscientific bias in favor of the private organizations listed and an arbitrary and capricious grant of privilege to the named private organizations to the exclusion of all others.

Finally, FDA's Guidance omits reference to the constitutional mandate in *Pearson*. The Guidance misleads the public and the regulated class to the extent that it suggests that a dietary supplement health claim not approved by FDA under its "significant scientific agreement" standard is prohibited on labels and in labeling. Under *Pearson*'s constitutional mandate, even if claims fail the "significant scientific agreement" test, FDA must nevertheless authorize all that are, at worst, potentially misleading with corrective disclaimers. *Pearson*, 164 F.3d at 659-660. Because the constitutional mandate interprets the First Amendment to the United States Constitution and the First Amendment is the higher law against which contrary law cannot stand, FDA must make clear to the regulated class within the Guidance that a claim it deems not backed by "significant scientific agreement" will nevertheless be authorized when a disclaimer can render it nonmisleading.

For these reasons, explained in detail below, FDA should promptly revise its Guidance. It should comply with the mandate of the United States Court of Appeals for the D.C. Circuit by explaining what it means by significant scientific agreement or, at minimum, what it does not mean. In that regard, FDA cannot rest upon the highly inexact and largely vacuous and variable statement that significant scientific agreement occurs after emerging science but before unanimous agreement. The universe described is immense, so immense as to exceed any reasonable definitional boundary. Indeed, nearly all scientific evidence falls between the polar extremes of emerging science and consensus. Accordingly, FDA should define with as much specificity as possible where on the continuum of scientific evidence between emerging science and consensus "significant scientific agreement" lies. Does it occur when a significant minority or segment of scientists who study the relationship agree that the claimed relationship is supported by the scientific evidence? Does it occur when at least half of the scientists who study the relationship agree that the claimed relationship is supported by the scientific evidence? Does it occur when at least three quarters of the scientists who study the relationship agree that the claimed relationship is supported by the scientific evidence? When may it be said on the continuum of scientific evidence that significant scientific agreement has been reached? In that regard, consistent with the dictates of Congress, FDA should hold that significant scientific agreement exists when

> a significant segment of scientists having relevant expertise agree, based on relevant scientific evidence, that consumers are *reasonably likely* to obtain the claimed health benefit.

Senate Report 103-410, at 24.

Congress determined that the above-quoted definition it supplied in committee is "consistent with the NLEA's goal of assuring that consumers have access on food and dietary supplement labels to health claims that are scientifically supported, without having to wait until the degree of scientific certainty contemplated by the drug standard has been achieved." *Id.* FDA's insistence on a higher standard, the equivalent of the drug certainty standard used as a condition precedent to grant of applications for new drugs, conflicts with Congress's intentions and cannot stand.

ARGUMENT

A. FDA'S GUIDANCE VIOLATES *PEARSON*'S APA MANDATE BY FAILING TO DEFINE "SIGNIFICANT SCIENTIFIC AGREEMENT"

The *Pearson* Court ordered FDA to "explain what it means by significant scientific agreement or, at minimum, what it does not mean." *Pearson,* 164 F.3d at 661. FDA's Guidance fails to comply. Nowhere in the entire Guidance does FDA provide any reasonable explanation of what it means by significant scientific agreement (or what it does not mean). The only "definition" for the term that the agency offers in the Guidance is one so broad, so vacuous, and so inexact as to be entirely unusable by the regulated class. Indeed, the extraordinary breadth of the definition suggests that any meaning FDA imparts to the term on a case by case basis may be the product of political discretion (or anti-dietary supplement bias) as much, if not more, than rational scientific judgment. In the Guidance, the agency states that, "[i]n the process of scientific discovery, significant scientific agreement occurs well after the state of emerging science, where data and information permit an inference, but before the point of unanimous agreement within the relevant scientific community that the inference is valid." Guidance at 16. That language embraces nearly the entire body of scientific evidence and does not afford the regulated

class sufficient information to discern where along the continuum of science between emerging data and consensus the point of significant scientific agreement exists. With the agency's definition, the regulated class certainly cannot discern the principles which guide FDA action (except that satisfaction of the drug certainty standard will probably suffice). Accordingly, the definition violates *Pearson*'s APA mandate to the agency. To comply with the mandate, FDA must revise its Guidance promptly as explained below.

B. FDA'S GUIDANCE VIOLATES *PEARSON*'S APA MANDATE BY NOT REVEALING THE PRINCIPLES WHICH GUIDE AGENCY ACTION ON CLAIMS SUPPORTED BY EVIDENCE OTHER THAN INTERVENTIONAL STUDIES BEARING PROOF OF DIRECT CAUSALITY

From the Guidance, one may discern that FDA has adopted a hierarchy to evaluate scientific evidence, placing at its top well designed interventional studies (and at the top of such studies randomized, controlled clinical trials). Although FDA's preference for well designed interventional studies is reiterated throughout the document, the FDA does not explain whether studies other than the very lengthy and expensive randomized, controlled interventional ones will suffice and, if other studies would, what comparative and cumulative weight FDA affords evidence other than randomized, controlled interventional studies. For example, from the Guidance it is impossible to determine whether FDA would ever accept as a substitute for randomized, controlled interventional studies, a combination of observational and mechanistic studies, or—if so—what kind of such studies would suffice to substitute for randomized, controlled interventional studies.

From the Guidance, one may discern that FDA demands that the regulated class supply it with proof that "a change in the dietary intake of the substance ***will*** result in a

change in a disease endpoint." FDA thus calls for conclusive proof of causality. FDA expects conclusive proof of causality regardless of the nature of the claim. Thus, a claim that a nutrient "may" reduce the risk of a disease or "may" reduce the symptoms of a disease is treated in the same manner as one that states a direct causal relationship (e.g., nutrient X will reduce the risk of disease Y, or nutrient X will reduce the symptoms of disease Y). Direct proof of causality is equal to that degree of proof required by this agency, pursuant to the "substantial evidence" standard, as a condition precedent to the grant of applications for new drugs. 21 U.S.C. § 355(e) (see generally *Weinberger v. Hynson Westcott & Dunning, Inc.*, 412 U.S. 609 (1973) and *E.R. Squibb & Sons, Inc. v. Bowen*, 870 F.2d 678, 679 (D.C. Cir. 1989).

FDA states that in evaluating the scientific evidence, it will require an affirmative answer to the following two questions: (1) whether the evidence in support of the substance/disease relationship outweighs that against it and (2) whether the evidence corroborates "that a change in the dietary intake of the substance ***will*** result in a change in the disease endpoint." Thus, in light of FDA's clear preference for randomized, controlled clinical trials and its insistence on direct evidence of causality, to the extent that a principle can be discerned from the Guidance, it is that FDA will authorize claims upon receipt of proof that they are corroborated by randomized, controlled clinical trials and upon receipt of proof of direct causality. That kind of near conclusive proof is the same as that required by FDA for approval of new drug applications. Accordingly, to the extent that FDA's Guidance reveals a principle to the regulated class it is one calling for a level of evidence Congress has unequivocally rejected in the context of health claims for dietary supplements. FDA must revise its Guidance. It must replace it with one that

complies with *Pearson*'s APA order and the dictates of Congress on interpreting "significant scientific agreement." The current Guidance fails on both accounts.

C. FDA'S GUIDANCE HARBORS AN UNSCIENTIFIC BIAS AND FAVORITISM FOR CERTAIN PRIVATE ORGANIZATIONS

In addition to its failure to explain what significant scientific agreement means (or, conversely, what it does not mean) in a manner that can enable the regulated class to discern the principles which guide agency action, the Guidance includes specific reference to a select group of private organizations. The reference gives equal weight to the opinions and recommendations of those organizations and the opinions and recommendations of federal government scientific bodies. Moreover, it fails to give equivalent weight to the opinions and recommendations of any other scientific body, e.g., any or all universities, other private scientific associations, and recognized authorities in the field of science. The agency offers no explanation for why the named private organizations (Committee on Nutrition of the American Academy of Pediatrics; the American Heart Association; and the American Cancer Society) should be given preferential treatment and status in the evaluation of health claims. For example, it does not explain (nor could it reasonably) why these private associations in particular are possessed of scientific insights, knowledge, and evidence superior to all others or why these private associations in particular should be viewed as equivalent to federal government scientific bodies. It is not at all unworthy of note that the American Heart Association and the American Cancer Society were amicus curiae in favor of the unsuccessful position articulated by the FDA in the *Pearson* case. Through that relationship, let alone all others between the FDA and those groups, FDA has engaged in legal and political battle against authorization of dietary supplement health claims. Thus,

far from serving as an unbiased source for opinion and recommendation, FDA has chosen precisely those entities that have a track record of partisan support for FDA's positions. For these many reasons, FDA's select listing of preferred private organizations in the Guidance constitutes arbitrary and capricious agency action and should be reversed in print as well as deed. The Joint Commenters do not object to agency acceptance of the opinion and recommendations of private scientific associations as sources of reputable information relevant to the evaluation of supplement-disease relationships, but the Joint Commenters strongly object to the arbitrary and capricious limited selection of three named associations made in the Guidance by FDA.

D. FDA'S GUIDANCE IS MISLEADING BECAUSE IT OMITS REFERENCE TO *PEARSON*'S CONSTITUTIONAL STANDARD AS AN ALTERNATIVE GROUND FOR AUTHORIZATION

The Director of the Center for Food Safety and Applied Nutrition has made it clear that FDA understands *Pearson*'s constitutional mandate to necessitate agency authorization of health claims even when those claims fail to satisfy its "significant scientific agreement" standard. Director Levitt wrote:

> . . . [W]e agree that the court's decision requires FDA to reconsider not only whether each of the four claims meets the significant scientific agreement standrd, but also, even if that standard is not met, whether the addition of a disclaimer to the claim could render it non-misleading. If the answer to either question is yes, we will authorize the claim.

See Exhibit A.

Indeed, the *Pearson* decision's constitutional mandate takes primacy over contrary agency rules and interpretations. It is, after all, the First Amendment which, under the Supremacy Clause, is the supreme law of the land. U.S.CONST. Art. VI. See also *Marbury v. Madison*, 5 U.S. 137, 180 (1803). Therefore, the complete omission of

the fact that a claim not authorized under significant scientific agreement may still have to be under the First Amendment is derelict of the agency. Indeed, the omission from the Guidance of reference to the *Pearson* Court's disclaimer requirement to protect First Amendment rights is a glaring one that renders the Guidance false and misleading. Its omission is material because regulatees may perceive that FDA's failure to authorize a claim under significant scientific agreement condemns the claim to indefinite suppression when, in fact, the constitutional duty of this agency is to authorize all, at worst, potentially misleading claims with corrective disclaimers. FDA must revise the Guidance to make clear to the regulated class that a claim it deems not backed by "significant scientific agreement" will nevertheless be authorized when a disclaimer can render it nonmisleading.

E. FDA'S GUIDANCE VIOLATES THE NLEA BY FAILING TO DEFINE "SIGNIFICANT SCIENTIFIC AGREEMENT" AS CONGRESS INTENDED

Congress has been severely critical of the way in which FDA has interpreted "significant scientific agreement." See Senate Report No. 103-410. In fact, Congress has documented the existence of an unscientific agency bias against dietary supplements and dietary supplement health claims that it has found wholly inconsistent with the intended meaning of "significant scientific agreement." The following are among Congress' findings on agency bias against claim approval:

> **In fact, the FDA has had a long history of bias against dietary supplements. S.Rep.No. 103-410, at 14 (1994).**
>
> **Mindful of the persistent evidence of FDA bias against dietary supplements . . . S.Rep.No. 103-410, at 30 (1994).**

Given the FDA's historical bias against dietary supplements. . . S.Rep.No. 103-410, at 31 (1994).

Despite a voluminous scientific record indicating the potential health benefits of dietary supplements, the Food and Drug Administration has pursued a heavy-handed enforcement agenda against dietary supplements for over 30 years. S.Rep.No. 103-410, at 14 (1994).

FDA's treatment of health claims on dietary supplements and its implementation of the health claims standard is hindering, rather than fostering, the dissemination of truthful and nonmisleading information about the nutrient/disease rleationship. S.Rep.No. 103-410, at 23 (1994).

The committee has heard multiple complaints that the FDA has been overly slow and rigid in considering and approving health claims for dietary supplements. S.Rep.No. 103-410, at 30 (1994).

FDA has applied [its health claims review standard] in a way that limits consumer access to important information on diet and health. S.Rep.No. 103-410, at 23 (1994).

The FDA has acted to restrict the information that the public may receive about dietary supplements. S.Rep.No. 103-410, at 16 (1994).

Despite the fact that the scientific literature increasingly reveals the potential health benefits of dietary supplements, the Food and Drug Administration has pursued a regulatory agenda, which discourages their use by citizens seeking to improve their health through dietary supplementation. S.Rep.No. 103-410, at 14 (1994).

In December, 1991, FDA proposed rules implementing the NLEA, but rejected all but one claim for supplements (for calcium/osteoporosis in White and Asian Women). Only one other claim has been approved since that time, the claim for folic acid and neural tube defects, and that claim was only approved after intense public pressure on the FDA. S.Rep.No. 103-410, at 15-16 (1994).

The preceding examples show how the FDA has tried to "protect" the public against "unsafe" products for which there is no evidence that the product is unsafe. The FDA has also acted to restrict the information that the public may receive about dietary supplements. Folic acid is a clear example. S.Rep.No. 103-410, at 16 (1994).

Beholden as it must be to Congress for its statutory authority, FDA has acted in a most peculiar manner. Rather than comply with the dictates of Congress, it has defied them. It

has chosen (against the express congressional command that it not do so) to articulate clearly only one sure way to achieve health claim approval (i.e., establish to FDA's satisfaction that a claim is backed by randomized, controlled clinical trials and direct proof of causation, to wit, establish satisfaction of the drug certainty standard). Congress plainly and unequivocally rejected the drug certainty standard for dietary supplement health claims. It has implored this agency to adopt a definition for significant scientific agreement far less stringent, a definition that FDA does not adopt in the Guidance. In committee Congress has made its expectations clear:

> **The Committee notes that the significant scientific agreement standard is, by design, more flexible than the standard established by law for FDA to review and approve drugs, which requires a demonstration of safety and effectiveness based on "adequate and well-controlled clinical investigations." While the intake of a nutrient on which a health claim is based must be safe, there is no requirement that health claims be derived from clinical trials, and, by its terms, the standard recognizes that scientific agreement on the validity of the claim does not have to be complete. Evidence from a broad range of reliable scientific sources should be considered in determining the adequacy of scientific support.**
>
> **In implementing the significant scientific agreement standard, FDA will be expected to take full advantage of the flexibility of the standard to maximize the availability on food and dietary supplement labels and labeling of disease-related information consumers can prudently use to affect their risk of disease.**
>
> **This includes recognizing that there will nearly always be some remaining scientific uncertainty about the validity of any diet-related health claim; that some individuals consuming or avoiding a nutrient in response to a health claim may benefit, while others may not; and that the benefits for any individual may consist not of absolutely avoiding a disease, but rather of reducing her or his risk of a disease.**
>
> **The end point for evaluation of the adequacy of support for a claim should not be definitive proof that the nutrient has the stated effect for all populations, but that the nutrient will produce the stated effect in the majority of a target population the majority of the time. In addition, the scientific evidence supporting a claim should not be held to the same standard used in evaluating new drug applications.**

> **Under the significant scientific agreement standard, the FDA should authorize claims when a significant segment of scientists having relevant expertise agree, based on relevant scientific evidence, that consumers are reasonably likely to obtain the claimed health benefit. This is consistent with the NLEA's goal of assuring that consumers have access on food and dietary supplement labels to health claims that are scientifically supported, without having to wait until the degree of scientific certainty contemplated by the drug standard has been achieved.**

S.Rep.No. 103-410, at 24.

Thus, FDA's Guidance has violated the intent of Congress by not defining significant scientific agreement as Congress ordered it to in Senate Report No. 103-410. FDA may not interpret significant scientific agreement to have a meaning contrary to that intended by Congress. Indeed, FDA's Guidance is wholly inconsistent with the intent of Congress on interpreting significant scientific agreement under the NLEA. Accordingly, that interpretation is invalid under *Chevron , U.S.A., Inc. v. Natural Resources Defense Council, Inc.,* 467 U.S. 837 (1984) because Congress has spoken to the precise matter in issue and the agency's interpretation is unreasonable in light of congressional intent.

F. JOINT COMMENTERS' RECOMMENDATIONS FOR REVISION TO THE GUIDANCE

The FDA must revise the Guidance if it is to survive judicial review. The Guidance fails to define "significant scientific agreement" as ordered by the *Pearson* Court. The Guidance indicates that a health claim is likely to be approved only if it is backed by randomized, controlled clinical trials and direct proof of causality. That benchmark is far higher than the one intended by Congress for dietary supplement health claims. Moreover, FDA has revealed an unscientific bias in favor of three private associations' opinions and recommendations. Finally, it has omitted from the Guidance the material fact that even if FDA deems a claim not backed by "significant scientific

agreement," it has a constitutional duty nonetheless to authorize even a potentially misleading claim with a corrective disclaimer.

To cure the many defects in the Guidance, FDA should: (1) define "Significant Scientific Agreement" as Congress intended, to wit: "**when a significant segment of scientists having relevant expertise agree, based on relevant scientific evidence, that consumers are reasonably likely to obtain the claimed health benefit;**" (2) should state where on the continuum of scientific evidence between emerging science and consensus "significant scientific agreement" exists consistent with Congressional intent; (3) should state clearly that it will not require the drug certainty standard of proof (i.e., randomized, controlled interventional studies and direct proof of causality) as a condition precedent to dietary supplement health claim approval; (4) should remove reference to the Committee on Nutrition of the American Academy of Pediatrics; the American Heart Association; and the American Cancer Society from the Guidance and make clear that it will not view those organization's opinions or recommendations as in any way more significant than the views of any other private scientific body or private scientific authority; and (5) should include reference to *Pearson*'s constitutional mandate and make clear that if a claim fails to satisfy FDA's "significant scientific agreement" standard it will be authorized nonetheless so long as the addition of a disclaimer can render it nonmisleading.

CONCLUSION

For the foregoing reasons, FDA should immediately discontinue reliance on the Guidance and revise it as recommended herein.

Respectfully submitted,

JULIAN M. WHITAKER, M.D.;
PURE ENCAPSULATIONS, INC.;
XCEL MEDICAL PHARMACY, LTD.;
MYCOLOGY RESEARCH LABORATORIES, LTD.;
DURK PEARSON and SANDY SHAW; and
AMERICAN PREVENTIVE MEDICAL ASSOCIATION,

By _____
Jonathan W. Emord
Claudia A. Lewis-Eng
Eleanor A. Kolton
Counsel for Joint Commenters

Dated: February 22, 2000

Exhibit A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington DC 20204

OCT 5 1999

Jonathan W. Emord
1050 Seventeenth Street, NW
Suite 600
Washington, DC 20036

Dear Mr. Emord:

This is in response to your letter of September 23, 1999. Your letter made several requests relating to FDA's Federal Register notice of September 8, 1999 (64 Fed. Reg. 48841), which solicited scientific data on the four health claims remanded to the agency in Pearson v. Shalala. Specifically, you requested that FDA (1) extend the time for submitting scientific data on the four claims until 75 days after the agency publishes its guidance on the significant scientific agreement standard; (2) confirm to you in writing and publish a correction notice in the Federal Register clarifying that FDA intends to consider whether the four claims may be authorized with a disclaimer even if the agency determines that they do not meet the significant scientific agreement standard.

With respect to your first request, we agree to extend or reopen the comment period on the September 8, 1999, notice for 75 days after the significant scientific agreement guidance is published. We agree that this is an example of when taking additional time is warranted. Be assured that the agency will give careful consideration to the data that it receives during the second 75 days.

As to your second request, we agree that the court's decision requires FDA to reconsider not only whether each of the four claims meets the significant scientific agreement standard, but also, even if that standard is not met, whether the addition of a disclaimer to the claim could render it non-misleading. If the answer to either question is yes, we will authorize the claim. We do not believe that a Federal Register correction notice is necessary, however. The September 8 Federal Register notice was only intended to solicit scientific data on the four remanded claims, not to describe the procedure and standard the agency will use to evaluate them. The notice stated that FDA was planning to reevaluate the scientific evidence for the claims "as a first step in complying with the court's decision." 64 Fed. Reg. at 48842 (emphasis added). Given the fact that the notice contained no errors and was not intended to explain the court's decision or set forth the agency's plans for implementing the decision, we see no need for a correction notice.

Your concerns about the notice and about statements in FDA's September 17, 1999, letter seem to stem at least in part from a misunderstanding about FDA's use of the word "authorize." By saying that the four claims must be "authorized" by FDA before they may be made in labeling, we meant only that the claims cannot be used unless and until FDA issues a regulation permitting them. We did not mean to imply that we would issue such a regulation only if the claims are found to meet the significant scientific agreement standard.

We hope that the above responds to your concerns.

Sincerely,

Joseph A. Levitt
Director
Center for Food Safety
and Applied Nutrition